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CONGENITAL EVENTRATION OF THE DIAPHRAGM*

OLIVER E. LAXDAL, M.D.,† HECTOR McDOUGALL, M.D.,‡ AND GILBERT W. MELLIN, M.D.§

NEW YORK CITY

SUCCESSFUL surgical treatment of diaphragmatic hernia dates back a great many years. However, it is only recently that congenital eventration of the diaphragm has been found amenable to surgery. Badenheur,[1] in 1879, performed the first laparotomy for congenital diaphragmatic hernia. In all the early reports and as recently as 1947 (Lattomus[2]) it was stated that surgery is not indicated in eventration of the diaphragm in infancy.[3] In the cases of eventration of the left leaf of the diaphragm reported below, 1 patient died, and autopsy was performed; the other was successfully treated by surgical operation. Since the literature on this condition abounds with mistaken ideas and inadequately founded conclusions, we believe that a review of the subject is warranted.

DEFINITION

Diaphragmatic "eventration" is generally regarded as a condition in which one leaf of the diaphragm balloons abnormally high in the chest and yet retains its continuity and normal attachments to the costal margins.[4-6] It may be either congenital or acquired. "Relaxatio diaphragmatica" is the term commonly applied to this condition in Europe.[7] Although the term "eventration" (*e*, out of, and *venter*, belly) is a misnomer, if its basic derivation is analyzed, its general acceptance warrants its continued use.[8]

HISTORICAL BACKGROUND

The posthumous works of Jean Louise Petit,[9] published in 1774, contain the first authentic description of a case of eventration. However, Beclard,[10] a few years later, was the first to apply the term eventration. Excellent reviews of this subject have been prepared by Bayne-Jones,[11] Korns[12] and Reed.[6]

In 1916 Wood[13] suggested surgical plication if the symptoms were sufficiently disabling and distressing. Morison,[14] seven years later, was the first to perform a successful repair of an eventration. His patient, a ten-year-old girl, was completely relieved of symptoms. Since that time about 20 cases of surgical repair of diaphragmatic eventration have been reported, mostly in adults.[15-17]

In 1945 Bisgard[4] reported the successful surgical repair of diaphragmatic eventration in a six-week-old infant, with complete relief of severe episodes of cyanosis. Since that time only 2 reported cases[18, 19] can be considered successful surgical repairs in infancy. In 1949 State[18] outlined a transabdominal technic for the successful repair of a right-sided eventration in a six-week-old infant. Butsch,[19] in the following year, described a successful repair of the left leaf of the diaphragm in a nine-day-old infant. Sullivan's[20] case recurred and required a second operation. Beck[15] recently reported the successful repair of a left-sided eventration in a child three years of age. Our Case 1, presented below, is the first reported case of successful surgical repair in infancy in which the diaphragm was thin, membranous and translucent throughout.

ETIOLOGY

In most cases eventration is the result of congenital insufficiency of the diaphragmatic musculature.[6, 11, 21] Except for the histologic appearance of the muscle and nerve, an identical condition may result from phrenic-nerve paralysis.[22-24] Large masses immediately below the diaphragm[25, 26] and intrathoracic lesions that cause pulmonary contracture[6, 27] may lead to an analogous clinical condition.[28] In many cases diaphragmatic eventration is discovered only after acute trauma,[29] a fall[13, 30] or any situation accompanied by a sudden marked increase in intra-abdominal pressure,[31] such as lifting,[32] pushing[33] or labor in child bearing.[34-36] In these cases a congenital diaphragmatic weakness probably existed before the trauma.

Thoma,[37] in 1882, was the first to suggest that most cases of eventration were congenital in origin.

*From the Department of Pediatrics, New York University, the Department of Surgery, New York University–Post Graduate Medical School, and the Fourth Surgical Service (New York University), Bellevue Hospital.

†Outpatient resident, Toronto General Hospital, Toronto, Ontario, Canada; formerly, chief resident in pediatrics, Children's Medical Service, Bellevue Hospital.

‡Surgeon, Sherbrooke General and St. Vincent de Paul hospitals, Sherbrooke, Canada; formerly, chief resident, Fourth Surgical Service, Bellevue Hospital.

§Assistant resident in pediatrics, Children's Medical Service, Bellevue Hospital.

In 1916 Bayne-Jones[11] offered considerable evidence in support of this thesis. The principal points in favor of this view are as follows:

Eventration has frequently been discovered in newborn infants and once in a fetus.[38]

Associated congenital malpositioning of the gastrointestinal tract, with abnormal mesenteric attachments, is common.[39, 40]

Other congenital anomalies are often associated with eventration — for example, congenital heart disease,[20] hypospadias,[12] cleft palate,[4] abnormal pulmonary segmentation,[11] ectopic kidney,[41] cerebral agenesis and blindness and deafness.[20]

The great preponderance of left-sided involvement is analogous to what is seen in congenital diaphragmatic hernia. Cutler,[42] in 1924, reported a thorough analysis of the embryology of diaphragmatic development. He concluded that "the vascular concentration in the region of the right side of the diaphragm would contribute to the strengthening and blocking of the pleuroperitoneal canal, while the atrophy of the common cardinal vein on the left would contribute to the weakening of the left half of the diaphragm."[30]

Failure to demonstrate degeneration, inflammation or other pathologic processes in the diaphragm or phrenic nerve in most cases also speaks for a congenital defect.[6, 21] The fact that synchronous motion is seen in about 50 per cent of cases is evidence that the phrenic nerve, at least in these cases, is intact. Careful isolation and sectioning of the phrenic nerve in Case 2 revealed no evidence of degeneration or recent trauma.

The majority of cases go unrecognized until adult life, when they are incidental findings on routine chest roentgenograms.[43-45] It is unlikely that such an extensive lesion could be acquired without a noteworthy incident of illness or accident.

Beck[21] considers congenital eventration to be a localized form of muscular aplasia, the origin of the defect being similar to that of clubfoot, congenital dislocation of the hip and arthrogryposis. He refers to an analogous condition in sheep in which the clinical picture of clubfoot or arthrogryposis may be combined with bilateral diaphragmatic eventration.

Incidence

No close estimate of the frequency of eventration would be possible unless routine x-ray examinations of the chest were made of a great number of newborn infants. Undoubtedly, a number of these patients die at birth or shortly thereafter, and the condition is detected only if x-ray films are taken or autopsy performed.

In 1935 Reed and Borden[6] found a total of 183 cases in the literature. To date, over 300 case reports have appeared. Reports of the frequency of eventration in routine mass chest surveys give a fairly accurate evaluation of the incidence in adults. Four recent reports of such surveys[43-46] revealed 46 cases of diaphragmatic eventration in a total of 457,048 roentgenograms. The incidence in adults is therefore roughly 1:10,000.

The sex incidence is approximately 2 cases in males for every 1 in females.[6, 47, 48] In an over-all review of the cases mentioned by Reed and Borden together with those subsequently reported the ratio of left-sided to right-sided eventration was 8:1.[49] We could find a record of only 1 case in which bilateral eventration was described.[50]

Pathology

Great variations are seen in the extent and pattern of muscular deficiency. All degrees exist from slight thinning out of the entire diaphragm to complete absence of muscle fibers, with only a thin, translucent aponeurotic sheet remaining. The excellent report by Bayne-Jones[11] includes the descriptions of 22 autopsied cases, in over half of which the diaphragm was thin, membranous and sac-like. In some cases the central tendon of the diaphragm appears broader and thinner than normal.[18, 50] In others there are muscle fibers in only one segment[19, 51] or scattered irregularly throughout the diaphragm.[11] Motzfeldt[52] and Fraenkel[11] reported the only 2 cases in which the muscle fibers on section appeared atrophied and fatty infiltration had occurred; unfortunately, reports of the histology of the phrenic nerves are not available in these cases.

The phrenic nerves at birth are usually normal or only slightly reduced in size.[6, 21] Degeneration or absence of phrenic-nerve fibers is rare when the condition has been present since birth. The lung on the affected side shows only failure of expansion, especially of the lower lobe.

Gastrointestinal malrotations, with abnormal mesenteric attachments, are frequent in this condition.[40] This is especially true of the stomach and duodenum, cecum[39] and splenic flexure. The stomach may lie in any one of the following positions, all of which are the result of its being drawn up into the chest (Fig. 1): normal position except that the fundus rises unusually high under the diaphragm[24] (Fig. 1*A*); inversion (partial or complete), with the greater curvature lying adjacent to the undersurface of the diaphragm[53-56] (Fig. 1*B* and *C*); and inversion, with partial or complete volvulus[40, 57] (Fig. 1*D*).

Symptomatology

Many patients are symptom free, whereas others die at birth or shortly thereafter as a result of acute cardiovascular and respiratory embarrassment. This is in keeping with the pathology. Probably half the patients with this defect are completely symptom free.[45, 58]

Symptoms occur when physiologic functioning of the cardiovascular, respiratory or gastrointestinal system is impaired through displacement or compression. From the standpoint of symptomatology, the cases are considered in two groups, as follows:

Acute Distress in the Neonatal Period

In the first few weeks of life there may be episodes of cyanosis, dyspnea and tachycardia.[6, 18, 59] Aptuated outward excursion of the costal margin on the affected side from failure of the diaphragmatic action to oppose the intercostal action) and absence of Litten's sign on the affected side (this is of no value in infancy because it is rarely seen normally but should be of some value in a tall thin child or an adult).

Absence of vocal fremitus over the lower part of the chest on the affected side is expected. The

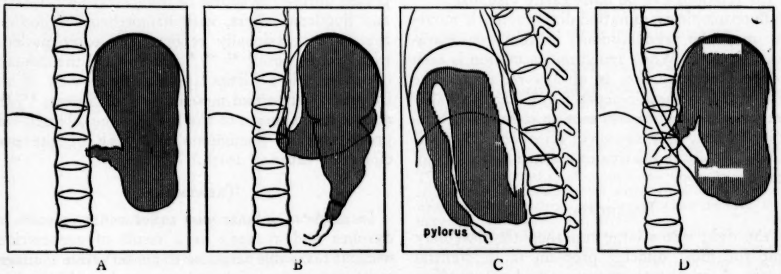


FIGURE 1. *Different Positions of the Stomach in Eventration of the Diaphragm. The fundus alone may rise up under the elevated left leaf, as in* A *(after Buckstein[21]). The pylorus may be drawn far over to the left, as in* B *(after Fichardt[23]). A biloculated type of stomach may be present, as in* C *(after Malenchini[24]). The stomach may be inverted, with partial or complete volvulus, as in* D *(after Ferriere[30]).*

propriate surgical correction will frequently save lives in this group.

Multiple Chronic Complaints in Adults[29, 57, 58]

In order of frequency these symptoms include a feeling of fullness and distress after meals, with belching of gas,[13] cough with wheezing, upper-quadrant pain and distress, with undue shortness of breath after exertion, pain going down the arm on the affected side[29] and severe hiccups.[60]

Some adults are symptom free until some incident occurs in which intra-abdominal pressure is suddenly greatly increased.[32, 33] Many patients in their fifties and sixties complain of undue shortness of breath for the first time. This is often the result of decreased efficiency of the intercostal and accessory muscles of respiration secondary to calcification of the thoracic cage.[6]

Physical Findings

It is almost impossible to make a diagnosis of eventration of the diaphragm on the physical findings alone. In most cases respiratory distress and dextrocardia suggest x-ray examination, which leads to a definitive diagnosis.

On inspection and palpation, the only features that are specific are Hoover's[61] or Korns's[12] sign (accen-apical impulse in left-sided eventration is either just behind or to the right of the sternum.

Percussion in left-sided eventration shows the area of cardiac dullness to extend to the right of the sternum. If the stomach and colon contain air a tympanitic note will extend high into the left side of the chest. If these viscera contain fluid an unusually dull note will result.[12] Auscultation may reveal bowel sounds in the chest, with diminished breath sounds over the affected side. The heart sounds in left-sided eventration are usually heard loudest to the right of the sternum.

X-Ray Findings

X-ray and fluoroscopic examinations are almost invariably the means by which the diagnosis is made. When adequate barium studies of the stomach and large bowel have been made, the diagnosis should rarely remain in doubt. In the posteroanterior projection the elevated diaphragm is seen forming a round, unbroken line arching from the mediastinum to the costal margin. In the lateral view both leaves of the diaphragm can be readily visualized, the affected one arching high into the chest. In the cases reported below, these two simple x-ray projections were diagnostic. How-

ever, when the upper margin is not clearly defined, barium studies provide the necessary information.

In the first place the stomach should be completely filled with barium, by means of a stomach tube if necessary. Films taken in the inverted position may be helpful if a suggestion of herniation is seen. When the stomach has been completely emptied of barium complete filling of the colon with a barium enema is desirable, the inverted position again being used if necessary. If the stomach can be slightly distended with air at this time the relations can be more easily visualized.

On fluoroscopic examination diaphragmatic movement may be synchronous, absent or paradoxical.[6, 11, 54, 62] When synchronous motion is seen the degree of excursion is always reduced. The possibility of a phrenic-nerve lesion can probably be excluded if synchronous motion is found. Paradoxical motion, the so-called Kienböck phenomenon,[63] is usually indicative of marked deficiency of muscle fibers.

Diagnosis

On the right side a large suprahepatic mass may present the most difficult problem in differential diagnosis. A subphrenic abscess, a hydatid cyst[26] or a large, loculated basal pleural exudate may present an identical radiologic picture. If bowel lies above the liver the problem can probably be decided conclusively with barium studies. Careful palpation should reveal any abdominal mass in the left upper quadrant that is large enough to produce upward displacement of the diaphragm.

Special diagnostic procedures that may be of help but should not be necessary include pneumoperitoneum,[64, 65] intragastric-pressure recordings[66] and phrenic-nerve stimulation.[67]

Pneumoperitoneum should rarely be necessary if good plain and contrast radiographic procedures have been carried out.[65] In cases in which pneumoperitoneum is being considered to rule out diaphragmatic hernia an exploratory laparotomy by a team ready to repair a hernia or eventration is probably the procedure of choice. Reed and Borden[6] give references to a number of serious complications that have resulted from pneumoperitoneum in eventration.[43] In proper hands, however, these dangers probably do not prevail today.[48]

Intragastric-pressure recordings have been reported to be helpful in ruling out diaphragmatic hernia. Intragastric pressure on inspiration will rise in eventration but will fall if a hernia is present. However, equivocal findings are common.[6]

Electrophrenic stimulation[67] should be helpful in diagnosis when no active diaphragmatic movement is seen on fluoroscopic study. If stimulation causes contraction, a defective phrenic nerve supply proximal to the site of stimulation can be postulated. Except at operation this procedure is helpful only if the suspected lesion lies above the clavicle. In diaphragmatic hernia contraction of muscle around the base of the sac is seen.

Prognosis

The extreme degrees of eventration are usually incompatible with life.[68] However, most children who survive the first few weeks should have little if any shortening of their life spans. Complications may occur. An acute episode of distress with cyanosis may follow an incident of stress or trauma. Complete rupture of the diaphragm has been reported during the course of induced labor.[6] Gastric and duodenal ulcers, with hemorrhage or perforation, are occasionally reported in adult patients with eventration.[16, 47, 58, 69] Volvulus of the stomach or mid-gut is a distinct possibility in view of the frequently abnormal mesenteric attachments.[57] Inadequate expansion of the lung on the affected side predisposes to pneumonia and may be the precipitating cause of death.

Treatment

In newborn infants who suffer acute episodes of dyspnea and cyanosis as a result of eventration, without favorable response to conservative management (oxygen, upright posture and so forth) surgical plication is always indicated, as in major degrees of diaphragmatic hernia. If a good response to symptomatic treatment occurs in these infants and they thrive without oxygen it may be wise to postpone surgery until the patient is about a year old. The degree of cardiovascular and respiratory distress is the major factor that should determine the optimum time for surgical correction.

In older children and adults, naturally, the degree of discomfort and disability caused by the disorder must be weighed against the ever-present though diminishing hazards of surgical repair. Conservative treatment when necessary consists chiefly of restricted activity and avoidance of heavy lifting. Lying in the face-down position has been reported to give relief from the discomfort that may occur after meals as a result of eventration.[17, 39] Belladonna derivatives have at times been found helpful in symptomatic treatment of gastrointestinal discomfort.[39]

Modern technics of thoracic surgery and anesthesia, together with the new antibiotics, have made surgery in this condition practical and often life saving. In most severe cases complete relief is impossible since the condition is essentially one of deficient musculature.

There are differences of opinion whether the abdominal, thoracoabdominal or thoracic approach should be used.[15, 17-19] We favor the thoracic incision because it allows better exposure of the lesion and hence greater ease and accuracy of repair.[51] Vital structures, which may be adherent to the dome of the diaphragm, may be damaged if the diaphragm is blindly pulled down for repair with

the abdominal incision. However, the abdominal approach permits visualization of the visceral relations and the opportunity to correct any gross malposition.

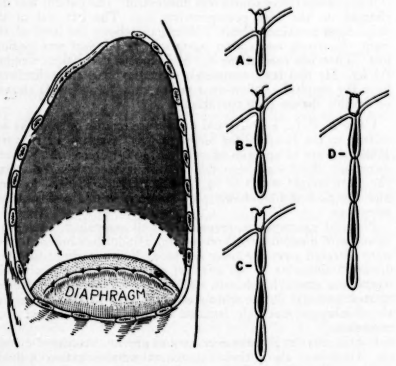


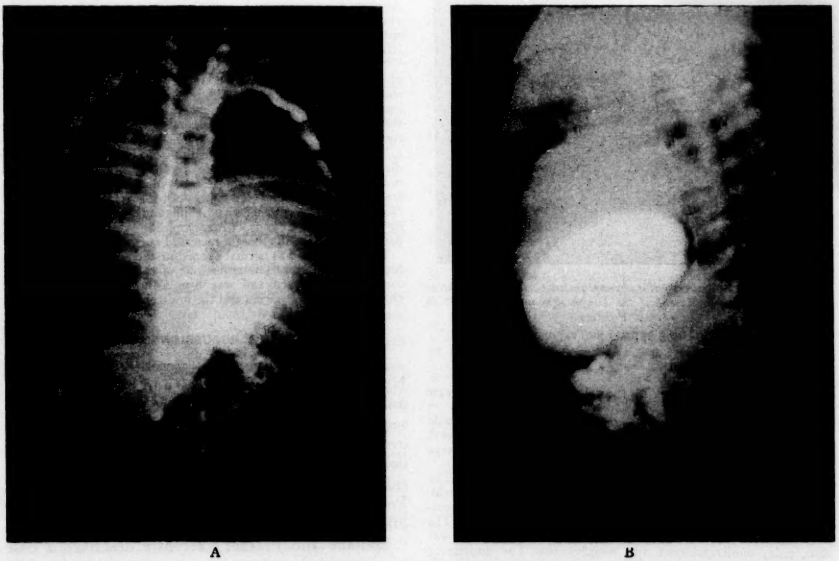
FIGURE 2. *Procedure for Imbrication of the Diaphragm.*

To date, no standardized operative technic has been devised. It is our belief that imbrication of the diaphragm by nonabsorbable suture materials in as many layers as can be placed without undue tension, should prove simple, safe and satisfactory (Fig. 2). In infants, when a very thin membranous diaphragm has been plicated, it is advisable to stress restricted activity until growth is complete, at the age of twelve to fifteen years. At this time a second surgical procedure should be seriously considered to reinforce the diaphragm and prevent diaphragmatic rupture during any acute stress or trauma. Monahan[16] recently reported the successful use of tantalum mesh for this purpose.

CASE REPORTS

CASE 1. J. J. was born at Bellevue Hospital on January 18, 1951. He was transferred to the Pediatric Service 13 hours later because of intermittent cyanosis and respiratory distress. The mother was a 17-year-old primigravida, and the prenatal course had been uncomplicated by any illness or accident. The labor and birth had been normal. The birth weight was 3.6 kg. The infant breathed spontaneously and promptly. However, intermittent cyanosis was noted almost from birth. The cry was weak, and breath sounds were diminished on the left. The color improved considerably with oxygen.

Physical examination revealed a normally developed, well nourished infant with a respiratory rate of 80 per minute. He was moderately alert and active, and there was no retraction of the chest. The heart sounds were loudest to the right of the sternum, where an area of dullness to percussion was also noted. Breath sounds were absent over the lower two thirds of the left side of the chest, but were readily heard above this.



A B

FIGURE 3. *Preoperative Roentgenograms in Case 1.*

Posteroanterior view (A), *after barium administration, demonstrates left-sided eventration, with dextroposition of the heart. Left lateral view* (B), *after barium administration, shows the shadow cast by the round, elevated left leaf of the diaphragm.*

X-ray examination of the chest demonstrated the classic picture of left-sided eventration. The left leaf of the diaphragm arched to the level of the fifth rib posteriorly (Fig. 3*A*). The heart, mediastinum and trachea were shifted to the right. On fluoroscopic examination the movement of the left leaf of the diaphragm was minimal, but synchronous. The stomach could be seen below the diaphragm, but was unusually high in the chest (Fig. 3*B*).

With constant oxygen and incubator care the patient's general condition improved, and a trial of conservative therapy was decided upon. At 4 weeks of age a number of studies of the upper and lower gastrointestinal tract with both barium and air contrast were carried out.[70] Fluoroscopic examination revealed that the movement of the left leaf of the diaphragm was no longer synchronous but had become paradoxical.

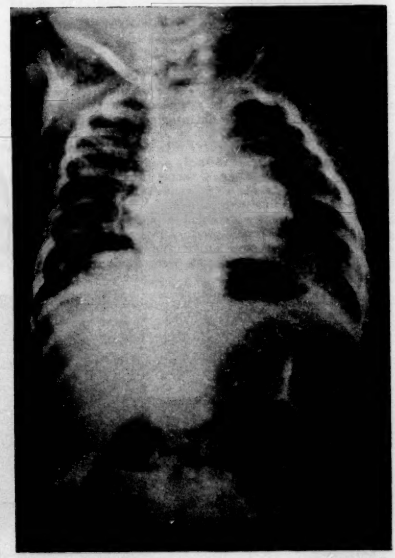


FIGURE 4. *Posteroanterior Roentgenogram in Case 1 after Operation, Showing the Left Leaf of the Diaphragm and the Heart in Normal Position.*

The left lung appears well expanded.

By the 7th week of life it was evident that the patient could not be maintained safely out of oxygen. His respiratory reserve was negligible, and it was feared that any strain on this reserve such as a respiratory infection might prove fatal.

On the 54th day of life surgical repair was carried out. The patient was placed in the true lateral position. Under cyclopropane anesthesia, with positive pressure, a standard thoracotomy incision was made through the 6th intercostal space. The diaphragm, which was intact throughout its entire extent, was thin, pale, semitranslucent and membranous. The underlying stomach and spleen could be clearly seen below. The left phrenic nerve was identified and did not present any abnormalities in its anatomic course or gross appearance. The lower lobe of the left lung showed evidence of partial collapse. The mediastinum was shifted to the right. The diaphragm was then plicated, 3 layers of cotton sutures being used (Fig. 2). These were placed without tension and seemed to bring the diaphragm down to its normal position. At the completion of this procedure, the left lower lobe, which had been held compressed during the repair, partially re-expanded. The thorax was closed by an interrupted cotton technic.

The postoperative course was uneventful. The patient was discharged on the 24th postoperative day. The left leaf of the diaphragm remained about 1 interspace above the level of the right. Fourteen weeks after operation the left leaf was motionless. When last seen at the age of 6 months the patient weighed 7.1 kg. He had been completely asymptomatic since discharge from the hospital. Follow-up x-ray examination (Fig. 4) showed no notable change since operation.

CASE 2. P. L., a 17-day-old premature female infant, was admitted to the Hospital for Sick Children, Toronto, in January, 1948, because of episodes of cyanosis and dyspnea of 24 hours' duration. Birth had been difficult owing to transverse arrest; the birth weight was 1.67 kg. Resuscitation had been prompt, and the patient had shown good progress until the day before admission.

Physical examination revealed a well nourished, premature infant with marked sternal retraction. Diminished breath sounds were detected over the lower left lobe. X-ray study of the chest disclosed elevation of the left leaf of the diaphragm, with air-containing stomach below it. Fluoroscopic examination demonstrated minimal but synchronous movement of the left leaf of the diaphragm; the right leaf, on the other hand, showed good excursion.

Continuous oxygen was necessary to prevent attacks of cyanosis. Treatment also included parenteral administration of fluids and penicillin. On the 9th hospital day surgical repair was being considered, but the patient's general condition seemed too precarious. Acute respiratory distress with cyanosis persisted until death on the 11th hospital day.

Post-mortem examination showed the mediastinum to be shifted markedly to the right, and there was considerable collapse of the left lower lobe. The dome of the left leaf of the diaphragm was seen to have ballooned into the left side of the chest, rising to the 3d interspace posteriorly. The stomach, spleen and splenic flexure of the colon were found high in the left side of the chest but below the diaphragm.

The diaphragm on the right was normal. The attachments of both leaves to the costal margins were normal. The left leaf was thinned out diffusely. The central tendinous areas of both leaves were normal in size, however. The muscular portion of the left leaf was approximately half the thickness of that of the right leaf.

The phrenic nerves were dissected from their insertions at the diaphragm to their origins in the cervical cord. They appeared normal in every respect. Sections were taken from the nerves, from the cervical cord and from both leaves of the diaphragm. No evidence of a degenerative or inflammatory process was seen in any of these sections. Microscopically, the muscle tissue of both leaves of the diaphragm appeared normal.

The right lung was normal except for the presence of extensive bronchopneumonia. The lower lobe of the left lung was almost completely collapsed and was firm as a result of pneumonic changes. All other viscera and the brain showed no abnormalities.

DISCUSSION

Partial eventration was recently described by Nylander,[71] Cuevas Ramirez[73] and Estevez[75]; Axler[74] and others[78] have suggested that this entity may be seen as frequently as if not oftener than complete eventration. Partial eventration is seen preponderantly on the right side and may be best considered an atypical form of diaphragmatic hernia. Pneumoperitoneum is especially helpful in the diagnosis of these cases.

Spillane and Prather[76] recently described a case of right-sided eventration in a four-year-old child that was successfully repaired surgically. They found the right kidney above the liver, and this feature added to the difficulty of operative repair. Consequently, they advised preoperative intravenous pyelography for cases of eventration com-

ing to surgery. Sanford,[77] in an excellent paper, reported another case of diaphragmatic eventration successfully repaired with the use of tantalum mesh.

Summary

Two cases of congenital left-sided diaphragmatic eventration in infancy are presented. Autopsy findings in 1 patient, who died at twenty-seven days of age, are reported; in the other the anomaly was successfully repaired by plication.

The entire subject of diaphragmatic eventration is reviewed, including the indications for and technic of surgical repair. The importance of recognizing the severe form of this condition in the newborn infant is stressed since surgical repair may be life saving.

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References

1. Iason, A. H. *Hernia: Historical evolution of hernial surgery, technical, medico-legal aspects.* 1325 pp. Philadelphia: Blakiston, 1941. P. 937.
2. Lattomus, W. W., and Winter, F. S. Diaphragmatic eventration: case report. *Delaware State M. J.* 19:14-16, 1947.
3. Clopton, M. D. Eventration of diaphragm. *Ann. Surg.* 78:154-163, 1923.
4. Biegard, J. D., and Robertson, G. E. Congenital eventration of diaphragm: surgical management. *Am. J. Surg.* 70:95-99, 1945.
5. Wood, W. B., and Wood, F. G. Congenital elevation of diaphragm, with reports on six cases. *Lancet* 2:392-397, 1931.
6. Reed, J. A., and Borden, D. L. Eventration of diaphragm. *Arch. Surg.* 31:30-64, 1935.
7. Wieting. Cited by Reed and Borden.*
8. Lerche, W. Insufficiency (eventration) of diaphragm: report of case. *Surg., Gynec. & Obst.* 34:224-229, 1922.
9. Petit, J. L. *Traité des maladies chirurgicales et des opérations qui leur conviennent.* Ouvrage posthume mis au jour par M. Lesne. 3 vol. Paris: T.-F. Didot jeune, 1774. Vol. 2. P. 266.
10. Cruveilhier. Cited by Reed and Borden.*
11. Bayne-Jones, S. Eventration of diaphragm: with report of case of right-sided eventration. *Arch. Int. Med.* 17:221-237, 1916.
12. Korns, H. M. Diagnosis of "eventration" of diaphragm: with report of case of aplasia of right lung and right half of diaphragm, associated with congenital dextrocardia. *Arch. Int. Med.* 28:192-212, 1921.
13. Wood, H. G. Eventration of diaphragm. *Surg., Gynec. & Obst.* 23: 344-348, 1916.
14. Morison, J. M. W. Eventration of diaphragm due to unilateral phrenic paralysis: radiological study, with special reference to differential diagnosis. *Arch. Radiol. & Electrother.* 27:353-364, 28:72-83 and 111-123, 1923.
15. Beck, W. C., and Pixley, C. Eventration of diaphragm in child. *Guthrie Clin. Bull.* 19:151-155, 1950.
16. Monahan, D. T. Eventration of diaphragm repaired with tantalum mesh. *New Eng. J. Med.* 244:475-477, 1951.
17. Deloyers, L., and van der Stricht, J. Les éventrations diaphragmatiques: constations radio-anatomo-cliniques; traitement. *Acta gastroenterol. belg.* 13:829-844, 1950.
18. State, D. Surgical correction of congenital eventration of diaphragm in infancy. *Surgery* 25:461-468, 1949.
19. Butsch, W. L., and Leahy, L. J. Technique for surgical treatment of congenital eventration of diaphragm in infancy. *J. Thoracic Surg.* 20:968-973, 1950.
20. Sullivan, R. B. Eventration of diaphragm: case report. *Clin. Proc. Child. Hosp.* 3:303-306, 1947.
21. Beck, W. C. Etiologic significance of eventration of diaphragm. *Arch. Surg.* 60:1154-1160, 1950.
22. Blattner, R. J. Unilateral paralysis of diaphragm without involvement of brachial plexus. *J. Pediat.* 20:223-229, 1942.
23. Koester, F. Zwerchfellhochstand in Kindesalter. *Röntgenpraxis* 7: 311-313, 1935.
24. Buckstein, J. *The Digestive Tract in Roentgenology.* 889 pp. Philadelphia: Lippincott, 1948. P. 743.
25. Caffey, J. *Pediatric X-Ray Diagnosis: A textbook for students and practitioners of pediatrics, surgery and radiology.* Second edition. 862 pp. Chicago: Year Book Publishers, 1950.
26. Jawara and Dumitresco-Mante. Cited by Reed and Borden.*
27. Labbé, M. Cited by Reed and Borden.*
28. Singer, H. A., and Boikan, W. S. Physiologic variations in contour of diaphragm simulating organic disease. *Am. J. Roentgenol.* 29: 601-606, 1933.
29. Wheatley, F. E. Report of case of eventration of left diaphragm. *Boston M. & S. J.* 197:87-91, 1927.
30. Hartzell, J. B. Traumatic segmental eventration of diaphragm. *U. S. Nav. M. Bull.* 45:323-327, 1945.
31. Allan, W. Cited by Reed and Borden.*
32. Bamber, J. M. Eventration of diaphragm. *M. Clin. North America* 2: 771-773, 1927.
33. Schneider, R. W., and Ernstene, A. C. Abnormalities of diaphragm. *S. Clin. North America* 21:1383-1398, 1941.
34. Feldman, L., Trace, I. M., and Kaplan, M. I. "Eventration" of right diaphragm: report of case with review of literature, chiefly from standpoint of etiology and diagnosis. *Ann. Int. Med.* 9:62-77, 1935.
35. Murless, B. C. Hernia of diaphragm as complication of labour. *Brit. M. J.* 2:251, 1947.
36. Comando, E. N. Eventration of diaphragm associated with pregnancy. *Am. J. Surg.* 79:857-860, 1950.
37. Thoma. Cited by Korns.[12]
38. Meckel. Cited by Zwanziger, H. L. In *De hernia diaphragmatica: dessertatio inauguralis medico-chirurgica.* 38 pp. Halae, 1819. P. 26.
39. Zellweger, H. Über zwei Fälle von angeborener Relaxatio diaphragmatica mit spezieller Berücksichtigung des Bauchsitus. *Helvet. paediat. acta* 2:227-241, 1947.
40. Ferriere, A. Splénomégalie congestive avec éventration diaphragmatique et volvulus gastrique. *Acta clin. belg.* 3:103-109, 1948.
41. Rosenfeld, D. H. Unusual type of inversion of stomach associated with diaphragmatic eventration and other anomalies. *Am. J. Roentgenol.* 52:607-610, 1944.
42. Cutler, E. C., and Cooper, H. S. F. Congenital deficiency of diaphragm. *Arch. Surg.* 8:506-523, 1924.
43. Lord, F. T. Eventration of diaphragm: diagnosis and treatment. *Arch. Surg.* 14:316-329, 1927.
44. Newcomet, W. S., and Spackman, E. W. Eventration and hernia of diaphragm as incidental finding. *Radiology* 27:36-43, 1936.
45. Kinzer, R. E., and Cook, J. C. Lesions of diaphragm with special reference to eventration and report of three cases. *Am. J. Roentgenol.* 52:611-615, 1944.
46. Chaudhuri, K. C., and Reddy, D. V. S. Eventration of diaphragm in childhood with report of case. *Indian J. Pediat.* 7:1-8, 1940.
47. Brailey, A. Discussion of Case Records of the Massachusetts General Hospital (Case 24252). *New Eng. J. Med.* 218:1074-1078, 1938.
48. Walton, H. J. Eventration of diaphragm. *Am. J. Roentgenol.* 11: 420-426, 1924.
49. Winkle, V. M. Abnormal position of liver, eventration of diaphragm, non-rotation of stomach, and intestinal obstruction with report of case. *Nebraska M. J.* 26:389-394, 1941.
50. Landon, J. F. Eventration of diaphragm. *J. Pediat.* 8:593-599, 1936.
51. Eggers, C. Hernia or eventration of diaphragm: report of case. *J. Thoracic Surg.* 1:41-49, 1931.
52. Motzfeldt, K. Cited by Reed and Borden.*
53. Fichardt, T. Eventration of diaphragm associated with inversion of stomach. *Clin. Proc.* 5:328-331, 1946.
54. Malenchini, M., and Roca, J. Hernia y eventratición diafragmática. *Dia méd.* 18:767-787, 1946.
55. Ekstrom, D. Symptomless eventration of diaphragm with inversion of stomach (report of two cases). *M. Woman's J.* 47:244-247, 1940.
56. Rhinehardt, D. A., and Rhinehardt, B. A. Congenital abnormalities of stomach: rare case. *Radiology* 7:492-497, 1926.
57. Hicks, F. G., and Harding, E. W. Two cases of diaphragmatic irregularities. *J. Canad. M. Serv.* 1:129-134, 1944.
58. Singleton, A. C. Eventration of diaphragm. *Brit. J. Radiol.* 10: 677-688, 1937.
59. Bisgard, J. D. Congenital eventration of diaphragm. *J. Thoracic Surg.* 10:394-491, 1947.
60. Mills, A. J. E. Case of eventration of diaphragm. *Brit. M. J.* 1:97, 1943.
61. Hoover, C. F. Functions of diaphragm and their diagnostic significance. *Arch. Int. Med.* 12:214-224, 1913.
62. Nicholas, F. G., and Nussbrecher, A. M. Right-sided eventration of diaphragm: with notes on case. *Lancet* 2:611-613, 1935.
63. Kienböck, R. Über Magengeschwüre bei Hernia und Eventratio diaphragmatica. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 21:322-332, 1914.
64. Faulkner, W. B., Jr. Diaphragmatic hernia and eventration: use of pneumothorax in differential diagnosis. *Am. J. Roentgenol.* 45:72, 1941.
65. Overholt, R. H. Diaphragmatic hernia: phrenic nerve stimulation under fluoroscope as aid in diagnosis. *Ann. Surg.* 91:381-391, 1930.
66. Schlippe, P. Physikalische Untersuchungen bei der Anwendung des Magenschlauches. *Deutsches Arch. f. klin. Med.* 76:450-473, 1903.
67. Sarnoff, S. J., Maloney, J. V., Jr., Sarnoff, L. C., Ferris, B. G., Jr., and Whittenberger, J. L. Electrophrenic respiration in acute bulbar poliomyelitis: its use in management of respiratory irregularities. *J. A. M. A.* 143:1383-1390, 1950.
68. Sakula, J. Congenital eventration of right half of diaphragm (specimen). *Proc. Roy. Soc. Med.* 33:629, 1940.
69. Quénu, J., and Fatou, E. Cited by Reed and Borden.*

70. Dissez, J., and Gillot. Un cas intéressant d'éventration diaphragmatique gauche. *J. de radiol. et d'électrol.* 27:427, 1946.
71. Nylander, P. E. A., and Elfvring, G. Partial eventration of diaphragm. *Ann. chir. et gynaec. Fenniae* 40:1-22, 1951.
72. Cuevas Ramirez, H. Sobre las relajaciones y las lobulaciones del diafragma. *Rev. méd. de Chile* 74:589-605, 1946.
73. Estevez, R. La relajación diafragmática derecha: importancia diagnóstica. *Rev. méd. de Chile* 74:644-647, 1946.
74. Axler, M., and Rehermann, R. L. Partial eventration of right diaphragm. *J. Pediat.* 42:320-324, 1953.
75. Beck, W. and Motsay, D. S. Eventration of diaphragm. *Arch. Surg.* 65:557-563, 1952.
76. Spillane, R., and Prather, G. Right diaphragmatic eventration with renal displacement: case report. *J. Urol.* 68:804-806, 1952.
77. Sanford, M. Eventration of diaphragm repaired utilizing tantalum mesh. *J. Thoracic Surg.* 25:422-428, 1953.

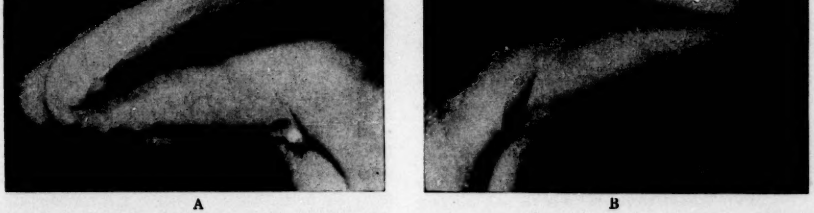
IDIOPATHIC VARICOSE VEINS OF THE UPPER EXTREMITY*

DONALD M. CLARK, M.D.,† AND RICHARD WARREN, M.D.‡

ANDOVER AND BOSTON, MASSACHUSETTS

THE term "varicose veins" customarily suggests, immediately, and almost exclusively, abnormal dilatations and tortuosities of the saphenous veins of the lower extremity. If one then stops to reflect where else in the body they may occur, the veins of the left pampiniform plexus, the esophagus and the inferior hemorrhoidal plexus are recognized as obvious, if less common, sites.

Varicosities of the veins of the upper extremity are rare and are usually provoked only by such considerable increases in venous pressure as are the result of arteriovenous fistulas of long standing or of obstruction by tumor or thrombosis to the great veins draining the limb. Primary spontaneous varices of the upper extremity are seen so infrequently as to be curiosities. Fourteen cases which can be considered to be of this type have been reported.[1-13] It seems fitting, therefore, to describe 2 additional patients who recently came under our observation.



A B

FIGURE 1. *Preoperative Appearance of the Veins of the Right* (A) *and Left* (B) *Upper Arms.*

CASE REPORTS

CASE 1. R. F. M. (W. R. V. A. H. 32209), a 21-year-old man, was admitted to the hospital on October 26, 1950, because of a swelling in each axilla of 3 years' duration. The symptoms were variable. At one time the mere presence of the swellings and the mild associated discomfort bothered him, and at another such heaviness of the arms and weakness that he found his work difficult. He had left military service 1 year previously. While he was on active duty he appeared to have had difficulty, because of these symptoms, in fulfilling tasks assigned him, and since then he had only been able to hold odd jobs because of discomfort.

The family history was noncontributory. None of his relatives had suffered from varicose veins. The past history was irrelevant. The patient had always been strong and healthy and had experienced no symptoms other than the presenting ones, except that he had "always been nervous."

Physical examination showed a normal, although somewhat agitated, man. The blood pressure was 128/80. In each axilla there was a 3-cm. bulbous, compressible swelling in the subcutaneous region that was characteristic of a localized venous dilatation. Communicating with it distally was a dilated basilic vein, which was abnormal in diameter throughout its entire extent to the lower forearm. In the forearm and the upper arm were many similar veins, the most noticeable being the cephalic vein in the forearm. The cephalic vein in the upper arm was not visibly dilated. The distribution of the dilatations was the same on both sides although their degree was more extensive on the right than on the left (Fig. 1). At no point were the veins tortuous. No edema, discoloration of the skin or telangiectasia was observed.

On the performance of various positioning tests it was noted that the veins were distended when the patient was either sitting or standing, regardless of the position of the arm. It was also observed that the veins were collapsed when he was lying down, regardless of the position of the arm. The direction of blood flow in the veins when they were distended was toward the heart since, on emptying and occlusion of a segment of vein with 2 fingers placed 8 cm. from each other, release of the lower finger alone caused the veins to fill immediately from below but on release of the upper finger they filled from above only down to the nearest valve.

*From the Veterans Administration Hospital, West Roxbury, Massachusetts, and the Monadnock Community Hospital, Peterborough, New Hampshire.

†School physician, Phillips Andover Academy, Andover, Massachusetts; member, Surgical Staff, Monadnock Community Hospital.

‡Lecturer on surgery, Harvard Medical School; chief, Surgical Service, Veterans Administration Hospital, West Roxbury.

In the recumbent position venous pressure with the needle in one of the dilated veins of the right forearm was equivalent to 10 cm. of water, and that in the left to 13 cm. The scalenus anticus test (hyperextension of the neck with rotation of the chin toward the side tested) had no effect on the venous distention and none on the arterial pulse. X-ray examination of the cervical spine showed no cervical rib. A venogram of the right axillary vein revealed only dilatation of the venous channels (Fig. 2). Visualization of the dye disappeared at the level of the first rib. Whether this was due to obstruction of the vein or dilution of the dye could not be made out. No more information was obtained when the venogram was done in the sitting position than in the lying.

Because partial obstruction to the venous drainage of the upper extremity by the clavicle and the 1st rib could not be excluded surgical exploration of the region was undertaken 19 days after admission. Through a supraclavicular incision the

FIGURE 2. *Venogram in Case 1, Showing Dilatation of the Right Axillary Vein.*

findings were entirely normal. There seemed to be no constriction in the region of the subclavian vein either by the first rib or by any other agent. It was impossible to make direct observations with the patient in the erect position. It was thought advisable to divide the anterior scalenus muscle in the hope that the 1st rib would drop down and relieve any possible obstruction to the vein in this region. This was therefore done, and the wound closed.

Postoperatively, there was no alteration in the size of the veins, and during the subsequent 3 months the patient stated that he had experienced no relief from the procedure.

Because of persistent discomfort in the axillas, which he stated to be disabling, he was readmitted to the hospital 2 months after discharge on January 31, 1951. Examination was unchanged from that on the previous admission. It was thought wise to do a local excision of the dilated veins in the right axilla.

On February 6 partial excision of the right basilic vein was carried out. The vein was exposed through a longitudinal incision in the axilla extending down the upper arm. It was excised from the middle portion of the upper arm to its union with the axillary vein, about 5 cm., as well as a small section (2 cm.) of the axillary vein, being removed. The brachial vein was divided in the process. Examination of the specimen and retrograde injection of physiologic saline solution into the distal cut stump of the basilic vein during operation established that the valves, although present, were, in that part of the venous system at least, incompetent. The valves in the brachial vein, however, were competent as demonstrated by similar attempted retrograde injection of fluid.

Gross examination of the excised specimen showed 1 valve to be present in each of the segments of axillary and basilic veins excised (Fig. 3). The valve leaflets appeared normal in all respects; their incompetency was therefore regarded as due largely to stretching of the valve rings.

The symptoms improved gradually after operation. When last seen 1¾ years after operation the patient was experiencing only slight discomfort in the arm and was working full time. It was of interest, however, that the symptoms in the left, untreated, arm had also either improved or become less significant to the patient. Examination showed that venous dilatations were still present below to the area of the operative incision but were much less pronounced than before operation. It

FIGURE 3. *Resected Specimen of the Axillary and Basilic Veins in Case 1, Showing the Presence of Valves.*

was also noted that the veins drained far more readily on elevation of the arm. The findings on the left side were unchanged. No further treatment was desired or thought necessary.

CASE 2. L. H. M. (M.C.H. 24758), a 27-year-old housewife, was admitted to the hospital on January 1, 1951, because of discomfort in the right arm and forearm of approximately 1 year's duration. At that time, while shaving the right axilla, she had noted a small, nontender mass in the region when she abducted her arm more than 90°. Shortly thereafter she observed moderate but definite discomfort, which radiated down the inside of her arm to the forearm and hand but which conformed to the distribution of no particular sensory nerve. Paresthesia was also experienced. The symptoms were produced only by abduction of the arm, when the small mass in the right axilla appeared, only to disappear as soon as the arm and forearm were adducted. As abduction was continued all discomfort increased. No pallor or rubor was noted in any position. There had been a slow increase in the size of the mass, which she described on admission as about the size of a walnut.

The past history was noncontributory except that, after an operation for herniated nucleus pulposus 3 years before, she had for several months worn an orthopedic brace that seemed to exert moderate pressure in the regions of both axillas. There was no history of trauma and no family history of varicose veins or hemangiomas.

Physical examination was negative except for the local lesion. The left axilla showed no abnormalities. The fact that the patient was thin made it easy to demonstrate the small tumor in the right axilla. No mass could be palpated with the arm at the side or when first abducted above the horizontal level. Within a few seconds after 90° abduction, however, a nontender mass, approximately 3 cm. in diameter, gradually appeared in the right axilla in relation to the lateral edge of the pectoralis major muscle. The patient then complained of moderate pain in the inner arm and general forearm accompanied by paresthesia. There was no abnormal color and no edema. Pulsations in the right radial, axillary and brachial arteries were within normal limits and maintained the same volume as those in the left upper extremity in a similar position. No unusual pulsations or bruits were noted.

Blood count and urinalysis were within normal limits. Blood serology was negative. Roentgenograms of the heart, lungs and thoracic and cervical vertebras demonstrated no abnormalities. There was no evidence of a cervical rib.

On January 8 the area of the right brachial axillary vein was explored under general anesthesia with the patient in a semi-sitting position and the upper extremity abducted. The tumor was exposed through a 15-cm. incision extending from the undersurface of the right arm across the anterior border of the axilla. The mass was found to consist of a venous sacculation approximately 3.0 by 2.5 cm. in relation to the junction of the brachial and axillary veins. The axillary brachial vein was ligated on each

side of the aneurysm, which was then completely removed. A nerve trunk, presumably the medial antibrachial cutaneous, approximately 5 mm. in diameter, was found coursing anteriorly over the aneurysm, which was also adjacent to the other major trunks posteriorly and on which it exerted direct pressure when the arm was in abduction. Even though the nerve trunks were handled with extreme caution, there was slight generalized weakness of the right arm and forearm and some steady paresthesia for 2 or 3 weeks after operation.

Gross examination showed a bulging segment of vein, fixed, purple gray, glistening, 1.9 cm. in diameter and 1.8 cm. long. There was a ligature at each end. Cross sections demonstrated solid, dark-red blood distending a thin-walled vein.

Microscopical examination revealed a distended, thin vein wall covering fresh blood. Elastic fibers were present in the wall.

The patient was discharged from the hospital 5 days after admission.

On September 30 she was again admitted to the hospital complaining of the same symptoms in the left axilla as had been noted on the right — namely, a small tumor mass when the left arm was abducted and moderate pain and paresthesia in the left arm and forearm. Physical findings were similar to those noted in the right axilla on the previous admission except that there were 2 small tumors in relation to the left axillary brachial veins.

FIGURE 4. *Appearance of the Axillary Brachial Vein at Operation on the Left Side in Case 2.*

The vein is ligated distally and proximally. The middle suture is being used as a retractor for the nerve (not seen in the photograph).

At operation on October 1 a situation similar to that on the right was found except that there were 2 sacculations, 1 of which was approximately 2.5 cm. in diameter and appeared to be in the axillary vein whereas the other, 4 cm. distal to it and approximately 2 cm. in diameter, involved the brachial vein (Fig. 4). Again, the main nerve trunks were noted to be so close that they were stretched when the aneurysms were distended. The involved vein was resected.

On gross pathological examination the specimen consisted of a segment of vein 7 cm. in length. It measured 0.6 cm. in diameter at one end and 0.3 cm. at the other end. In the center it was dilated to 1.5 cm. in diameter. One tributary entered its midportion. Section disclosed an extremely thin wall. In the midportion there was a valve with no gross changes.

Microscopical examination revealed a very thin wall. The tunica media was poorly developed. Elastic tissue in the adventitia was scant. No changes were seen in the intima.

The patient was discharged without complications 5 days after admission. There were no further symptoms involving the left axilla.

After the 2d discharge from the hospital, the patient was perfectly comfortable for about 2 months, or until 3 months before the 3d admission on March 24, 1952, when she again noted symptoms referable to the right axilla, the original area involved. These consisted of pain referred down the right arm and forearm on abduction of the arm and an increasing tumor mass, apparently larger than that noted at the 1st operation. For the 1st time there was continuous discomfort in the right arm and forearm, even when the arm was held close to the side.

Physical examination demonstrated a larger mass than before. It occupied a large part of the depths of the right axilla and, as before, gradually increased when the arm was elevated and abducted. When this position was maintained a sharp pain radiated from the axilla down to the elbow along the inner aspect of the arm, with increasing numbness and tingling along the dorsal aspect of the forearm and the hand, including all the fingers. There were old healed scars in the left and right axillas. No mass was present in the left axilla. Radial pulses were bilaterally equal. The radial pulse diminished markedly on raising of the right arm. There was no sign of muscular atrophy in either hand or arm and no significant weakness in the right arm as compared with the left. Nor were changes in sensation pain, touch or temperature demonstrable.

At operation on March 25 a sacculation was found that was approximately 4 by 5 cm. in diameter and occupied almost the entire depth of the axilla. It terminated approximately 1 cm. distal to the rib cage. In the lateral wall of the freed, greatly distended vein the black silk suture used when the first right axillary segment had been removed could be seen. At that time the suture had been applied to a normal-appearing vein. What had occurred after the operation was that the remaining stump of the normal-appearing axillary vein had become a large venous "aneurysm" extending almost to the rib cage.

It was thought at the beginning of the operation that the mass could be removed without any further exposure, but it became evident that there were so many large tributaries entering the area involved in the brachial plexus that additional exposure was necessary. Accordingly, the pectoralis major muscle was dissected free of its attachment to the head of the humerus, after which it was possible to ligate the aneurysm flush with the wall of the thorax. Although every effort had been made not to injure the brachial plexus it was impossible not to press upon it because of its intimate connection with the mass.

Gross examination disclosed a segment of vein measuring 9 cm. in length tied at each end. The lumen in the midportion varied from 0.7 to 1.5 cm. in diameter. Section revealed an extremely thin wall, with lumen filled with blood clot.

Microscopical examination showed a markedly thin wall composed of endothelium and loose fibrous tissue and scattered muscle fibers.

The patient was discharged 11 days after admission, with almost complete paralysis of the right upper extremity. Sensation gradually returned to the hand and forearm, and there was steady, continuous return of function, which was fair after 5 months and complete after 7 months.

Eight months after the last operation there was perfect function of the right upper extremity, except that hyperabduction was limited by about 5°. There had been no recurrence in the partially resected left axillary vein.

DISCUSSION

Although Pitha[1] and Palmgrén[2] both reported cases of congenital vascular dilatations of the upper extremity confined to the venous system, Bockenheimer[3] made the first attempt to classify this and other closely related conditions. He stated that such venous abnormalities must be distinguished from racemose or cirsoid dilatations of a pure arterial origin and from those of combined arterial and venous nature called by Weber[14] "diffuse phlebarteriectasia." He, after Weber, gave it the name of "idiopathic diffuse phlebectasia." Bode[10] went farther in classification and attempted to differentiate dilatations that were tumors and had been called by Virchow[15] "Venöse Rankenangiom" and the simple dilatations of Bockenheimer.

In a review of the reported cases, however, it was not easy to confirm Bode's distinction. Of the

16 cases recorded, including the 2 presented above, reports on 11 are available in sufficient detail for analysis. They do, indeed, fall into two general groups: those with extensive dilatations of all veins in all layers of the limb or part of limb, associated with phleboliths, muscle atrophy and disability; and those with dilatations of localized areas of the venous system involving merely major venous trunks. Neither of these groups, however, can definitely be established as being or not being neoplastic, and there is no evidence that they are not different stages of the same disease.

There were 5 cases in the first, or extensive, group and 6 in the second, or localized, group, which includes the 2 reported above. Two of the 6 patients in the latter group had more extensive involvement than the other 4; however, 1 of them had phleboliths, and this case may have represented a "transition" or "borderline" stage between the two types.

All the patients but Bockenheimer's,[3] who was fifty-two, were twenty-six years of age or under at the time of the first symptom. That 3 were females and 8 males is probably insignificant since 2 of the 5 not included in the 11 analyzed are known to have been females.

In 9 patients there was unilateral involvement — on the left side in 3 and on the right in 6. Although 1 of the other patients suffered from a similar condition simultaneously in the lower extremity the 2 cases presented above are the only ones so far reported with bilateral involvement of the upper extremity.

The presence or absence of phleboliths appears to be determined by the diffuseness and degree of the involvement of the smaller veins. Phleboliths were not observed in either of our patients.

In all but 1 of the previously reported cases some enlargement of the affected arm over the opposite one was noted, but in only 2 was frank edema mentioned. No abnormal size or swelling was present in our patients, although the bilateral involvement might make it difficult to evaluate some increase in size over that which would have been normal for the person concerned.

Similar varicosities may occur in the lower extremity, and idiopathic diffuse phlebectasia has been reported. Such cases are not reviewed in this report. Also excluded are 1 or 2 cases included in previous reviews that on further study appeared to have a phlebitic origin.

Venography in this condition has not previously been reported. In both our patients there seemed to be some obstruction to the contrast substance at the level of the first rib when the arm was held in abduction. Since this occurs to varying degrees in the normal person, it is undetermined what part such a mechanical factor plays in etiology.

Treatment in the 9 cases mentioned above was conservative, with or without bandaging in 4, x-ray treatment in 1, x-ray treatment followed by excision in 1 and excision alone in 3. In 1 case it was considered wise to remove the radial artery as well since an arterial element was suspected. Gangrene of a digit and amputation of the extremity followed, with death from secondary hemorrhage and sepsis a month later. Pathological examination showed the disease to be confined to the veins. Of the 2 other patients on whom excision was done recurrence quickly followed in 1, and the other was greatly relieved although the reported follow-up period was short. The case of excision that followed x-ray therapy was also, apparently, successful.

Little can be said about etiology except that its occurrence in young people strongly suggests a congenital defect. We agree with Sonntag[5, 7] that this defect is probably a weakness of the venous wall or its supporting structures. Valves were definitely present, though incompetent, in both our cases, the incompetence presumably being due to dilatation of the valvular ring. The element of chronic obstruction at the thoracic inlet as suggested by venography cannot be excluded. But scalenotomy had no effect in Case 1 although it is perhaps too much to expect such a dilatation to recede completely after an obstruction has been relieved. The recurrence on the right side after complete resection in Case 2, however, is a point in favor of the obstruction theory. It is perhaps reasonable to suppose that, whereas most of the cases referred to in the literature were of congenital origin, in the 2 cases reported above both factors — congenital weakness of the venous wall and partial venous obstruction — were responsible. As a parallel may be cited the well known occurrence of varices in the lower extremities of certain athletes that have been attributed to the effects of the increased blood flow of physical exertion superimposed on congenital weakness of the venous wall.

During the last ten years increasingly critical evaluation of brachial "neuritis" has been evident, especially since the recognition of the syndrome of rupture of both cervical and lumbar disks, together with more detailed knowledge of the variations of the brachialis syndrome and pain in the upper extremity caused by protracted and unusual positions of the shoulders and arms.

Slight to severe recurrent or steady pain in the thorax, shoulder, arm and forearm and hand, in some combination and in some cases associated with symptoms based on vascular combination, have repeatedly been described. A partial list of the many conditions and diseases responsible for such pain includes systemic disease such as infectious polyneuritis; myocardial infarction, direct trauma to the shoulder and axilla; menopause; slumping of the shoulders in middle age; arthritic spurs involving the cervical vertebras; spinal-cord tumor; ruptured cervical intervertebral disk; thrombophlebitis of the axillary brachial veins; com-

pression of the neurovascular bundle between the first rib and the clavicle, with or without cervical rib or fractured clavicle (brachialis syndrome); "shoulder-bracing" syndrome of soldiers carrying heavy packs; and the abduction and external rotation syndrome of those who sleep with their hands under their heads. To this list might be added simple dilatation of the axillary brachial veins, which was especially striking in Case 2.

Summary

Two cases of bilateral dilatation of the veins of the upper extremities are described.

Although the factor of costoclavicular compression cannot be excluded it seems unlikely, and it is suggested that the primary etiology of the condition is a congenital weakness of the venous walls.

One more condition is indicated, easily overlooked in the obese, that can produce referred upper-extremity pain and paresthesia from shoulder to fingers.

References

1. von Pitha, F. Die Krankheiten der Extremitäten. In *Handbuch der allgemeinen und speciellen Chirurgie.* Edited by F. von Pitha and A. T. Billroth. Vol. 4 (2B). Erlangen: F. Enke, 1869. Pp. 1-380.
2. Palmgrén. Cited by Sonntag.[7]
3. Bockenheimer, P. L. Über die genuine diffuse Phlebektasie der oberen Extremität. In *Festschrift für Georg Eduard von Rindfleisch.* 619 pp. Edited by M. Borst. Leipzig: Engelmann, 1907. Pp. 311-338.
4. Bircher, E. Genuine Phlebektasie des Armes. *Arch. f. klin. Chir.* 97:1035-1042, 1912.
5. Sonntag, E. Genuine diffuse Phlebarteriektasie und Phlebektasie. *Ergebn. d. Chir. u. Orthop.* 11:138-182, 1919.
6. Schmidt, A. Genuine diffuse Phlebektasie am Arm. *Deutsche Ztschr. f. Chir.* 198:403-410, 1926.
7. Sonntag, E. Über einen Fall von genuiner diffuser Phlebektasie an Unterarm und Hand. *Arch. f. klin. Chir.* 153:802-807, 1928.
8. Akaiwa, K. Diffuse phlebectasia of left arm. Cited by Freund.[9]
9. Freund, E. Diffuse genuine phlebectasia: report of case. *Arch. Surg.* 33:112-121, 1936.
10. Bode, H. G. Über die genuine diffuse Phlebektasie insbesondere über ihre Beziehungen zum arteriellen und venösen Rankenangiom sowie zur genuinen diffusen Phlebarteriektasie. *Med. Klin.* 33: 1164-1170, 1937.
11. Aliçli, S. Cited by Kert, M. J., and Grishman, A. J. Diffuse genuine phlebectasia. *J. Mt. Sinai Hosp.* 11:278-281, 1945.
12. von Szeleczky, G. Über angeborene, umschriebene Erweiterungen der Vena axillaris. *Zentralbl. f. Chir.* 68:1686-1691, 1941.
13. Candel, S. Varicose veins of upper extremity: report of two cases. *U. S. Nav. M. Bull.* 44:1052-1059, 1945.
14. Weber, O. Von den ästigen Pulsadergeschwülsten, dem Aneurysma cirsoideum und anastomoseon (racemosum) oder dem sog. Varix arterialis und dessen Combination mit Phlebectasieen. In *Handbuch der allgemeinen und speciellen Chirurgie.* Edited by F. von Pitha and A. T. Billroth. Vol. 2. Part 2. Erlangen: Enke, 1869. Pp. 154-162.
15. Virchow, R. Angiome. In *Die krankhaften Geschwülste.* Vol. 3 (1). Berlin: Hirschwald, 1865. Pp. 306-496.

GAMMA GLOBULIN

Effect on Secondary Attack Rates in Infectious Hepatitis

Alta Ashley, M.D., M.P.H.*

Augusta, Maine

During the period January 1, 1952, through April 15, 1953, 671 cases of infectious hepatitis were reported to have occurred in Maine. This was far in excess of the number known to have occurred over a similar previous period though no true incidence was known before 1948, when the disease became reportable. In 1947 a small localized epidemic, involving an estimated 100 cases, had appeared in the southwest portion of the State. In 1949, the first full year of reporting, 17 cases were reported; there were 7 cases in 1950 and 21 in 1951.

Table 1. *Age-Specific Rates during an Epidemic of Infectious Hepatitis.*

Age	Rate per 100,000
yr.	
<5	35
5-9	214
10-14	199
15-19	87
20-44	68
45+	75

The incidence was somewhat higher during the first six weeks of 1952, cases occurring chiefly in seaport areas such as Portland, Belfast and the Bangor-Brewer areas. By the middle of February 19 cases had been reported — 13 from Portland alone

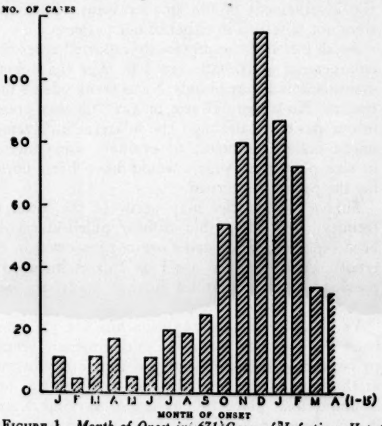


Figure 1. *Month of Onset in 671 Cases of Infectious Hepatitis. In 13.7 per cent of cases the date of onset is unknown.*

By the beginning of July 80 cases had been reported, and at the end of September the number had risen

*Special assistant to the director, Bureau of Health, Maine Department of Health and Welfare.

to 134; a full-blown epidemic was in progress. At that time a plea for the use of gamma globulin among susceptible household contacts was issued by the Bureau of Health to all practicing physicians and osteopaths, and to local health officers. Detailed epidemiologic reports were made on each newly occurring case and on as many previously reported cases as possible. All but 92 cases were so investigated, and in 235 households, including 388 cases, this investigation was carried out at least one month after the onset of the last case in the family.

Distribution of the 671 cases between the sexes was about equal — 323 males and 348 females. The greatest number of cases (414) occurred in persons under twenty; 35 patients were under five, 176 between five and nine. 142 between ten and fourteen, and 61 between fifteen and nineteen years of age; 212 were twenty to forty-four years of age, and 31 were over 45. The ages were not known in 14 cases.

Age-specific rates are presented in Table 1.

School-age children had the highest rate of incidence. In fact, 159 of the 269 cases and 59 of the 119 secondary cases, among the 235 families investigated, occurred in children five to fourteen years of age. A schoolmate was frequently named as the only known source of infection.

The epidemic increased more or less gradually until October, rising rapidly to a peak in December (Table 2 and Fig. 1). The subsidence was more rapid than had been expected, and it was believed that the use of gamma globulin may have altered the natural progress of the epidemic. Presumptive evidence of this was furnished by South Portland. Early in December 11 cases of hepatitis occurred in two classrooms in the elementary schools. On December 19 gamma globulin was given to all exposed members of these classrooms and to their household contacts of preschool age. Fifty-two children received gamma globulin in doses calculated as 0.01 cc. per pound of body weight. No further

TABLE 2. *Month of Onset of 671 Cases of Infectious Hepatitis, According to Age.*

	Month	Patients under 5 Yr.	Patients 5–9 Yr.	Patients 10–14 Yr.	Patients 15–19 Yr.	Patients 20–44 Yr.	Patients over 45 Yr.	Patients of Unknown Age	Totals
(1952)	Jan.		1	3	1	4			9
	Feb.			1		3			4
	Mar.		3	4	1	1			9
	Apr.	1	8	3		4	1		17
	May		3			2			5
	June	2	4	3		2			11
	July	2	5	1	3	9			20
	Aug.		8	3		8			19
	Sept.	3	3	6	5	8			25
	Oct.	5	14	10	6	15	3	1	54
	Nov.	2	20	15	7	31	4	1	80
	Dec.	6	40	18	16	34	1		115
	Unknown	2	13	6	5	28	10	6	70
(1953)	Jan.	5	31	23	2	22	4		87
	Feb.	3	14	27	7	17	4		72
	Mar.	2	6	13	3	11	1		36
	Apr.	2	2	3	4	4		1	16
	Unknown		1	3	1	9	3	5	22
Totals		35	176	142	61	212	31	14	671

TABLE 3. *Age Distribution of Patients with Infectious Hepatitis and Recipients of Gamma Globulin (235 Families).*

Age	Initial and Simultaneous Cases	Susceptible Household Contacts	Contacts Not Inoculated	Contacts Inoculated	Patients with Secondary Cases Receiving Globulin		Patients with Secondary Cases Not Receiving Globulin	
					Number	Attack Rate %	Number	Attack Rate %
<5	14	190	124	66			16	12.9
5–9	93	196	132	64	2	3.1	31	23.5
10–14	48	131	102	29	1	3.4	25	23.5
15–19	23	62	48	14			14	29.1
20–44	85	315	235	80			27	11.5
45+	6	65	49	16			3	6.1
Totals	269	959	690	269	3		116	
Averages						1.1		16.8

cases developed in these grades or in the families affected.

Effect of Gamma Globulin on Secondary Attack Rates

To study the effect of gamma globulin on the secondary attack rates it was necessary to have epidemiologic reports at least thirty days after the occurrence of the last case in a household. Such reports were made on 235 families, and data so obtained form the basis of discussion in this paper. There were 14 other families in which 57 out of 58 susceptible contacts presumably received gamma globulin. No cases were reported from these families in persons receiving globulin, but they are excluded from the discussion because epidemiologic investigations were not repeated after globulin had been given.

Globulin was given to 1 or more household contacts in 67 of the 235 households. Of the total 976 household contacts in these families 268, or 27.6 per cent, were inoculated. Three hundred and eighty-eight cases of hepatitis were reported from the 235 households; 269 of these were initial (or simultaneous with an initial case), and 119 were secondary. The onset of secondary cases ranged ten days to six months after the last household case. Patients with onset intervals of less than ten days were considered to have been infected from the same source and at the same time as the patients with the so-called primary cases and were therefore designated as simultaneous; there were 33 such cases.

Only 3 of the 119 secondary cases occurred in contacts to whom gamma globulin had been given early enough to have been a factor in prevention. Two of these occurred thirty-five and 1 thirty-six days after inoculation — thirty-five, forty-two and forty-six days, respectively, after onset of the last household case. Two were described as "mild cases"; the third patient could not be found for verification. In 3 other cases in which globulin was given the disease developed within forty-eight hours, and a fourth patient received globulin therapeutically on the day of onset. In these 4 cases, which have not been included in the total of cases protected, globulin injection had no noticeable ameliorating effect.

The over-all attack rate was 16.8 per cent for noninoculated and 1.1 per cent for inoculated contacts (Table 3). These figures differ somewhat from those obtained when cases were divided into families because of 4 cases, discussed below, that

Table 4. *Effect of Family Size and Gamma Globulin on Secondary Attack Rates in 235 Families.*

Susceptible Members in Family	No. of Families Concerned							
	no secondary cases	1 secondary case	2 secondary cases	3 secondary cases	4 secondary cases	5 secondary cases	6 secondary cases	7 secondary cases
Total 235 families:								
0	3							
1	14	1						
2	18	2	1					
3	50	13	1					
4	34	10	2					
5	25	9	3			1		
6	14	9		2	1			
7	3	3		1	2	1	1	1
8+	4	1	2	3				
Totals	165	48	9	6	3	2	1	1
168 unprotected families:								
0	3							
1	10	1						
2	14	1	1					
3	24	13	1					
4	23	9	2					
5	16	8	3			1		
6	8	9		2	1			
7	2	2		1	1	1	1	1
8+	3	1	2	3				
Totals	103	44	9	6	2	2	1	1
46 protected families:								
0	0							
1	4							
2	4							
3	19							
4	6							
5	7							
6	4							
7	1	1						
>7	0							
Totals	45	1						

occurred in partially protected families. Bennett et al.[1] reported failure to protect 1 out of 36 with globulin — that is, an attack rate of 2.8 per cent.

It might be said that since gamma globulin was administered often only after at least 1 secondary case had occurred, some of the remaining contacts were probably immune and that a falsely low secondary attack rate was thus obtained. Excluding families not given globulin immediately there were 61 households in which 188 persons were inoculated.

studied (Fig. 2). Families were arranged according to the number of susceptible persons in the household. The range was from 0 to 11, the greatest number of families — 64, or 27.2 per cent — containing 3 susceptible members. The greatest number of susceptible persons was in families with 3 to 5 susceptible members. Secondary cases occurred among all families except the 1 in the series containing 8 susceptible members and, of course, the 3 families in which there were none. A previous

TABLE 4 (*Concluded*).

SUSCEPTIBLE MEMBERS IN FAMILY	TOTAL FAMILIES	TOTAL FAMILIES WITH SECONDARY CASES	PERCENTAGE OF FAMILIES WITH SECONDARY CASES	TOTAL SECONDARY CASES	TOTAL SUSCEPTIBLE CONTACTS	SECONDARY ATTACK RATE
Total 235 families:						%
0	3	0	0.0	0	0	0.0
1	15	1	6.7	1	15	6.7
2	21	3	14.2	4	42	9.5
3	64	14	21.8	15	192	7.8
4	46	12	26.1	14	184	6.5
5	38	13	34.3	20	190	10.5
6	26	12	46.3	19	156	12.2
7	12	9	75.0	32	84	38.1
8+	10	6	60.0	14	96	14.6
Totals	235	70		119	959	
Averages			29.8			12.4
168 unprotected families:						
0	3	0	0.0	0	0	0.0
1	11	1	0.9	1	11	9.1
2	16	2	12.5	3	32	9.4
3	38	14	36.9	15	114	13.2
4	34	11	32.3	13	136	9.6
5	28	12	42.7	19	140	13.6
6	20	12	60.0	19	120	15.9
7	9	7	77.8	27	63	42.9
8+	9	6	66.7	14	86	16.3
Totals	168	65		111	702	
Averages			38.6			15.8
46 protected families:						
0	0	—	—	—	0	—
1	4	—	—	—	4	—
2	4	—	—	—	8	—
3	19	—	—	—	57	—
4	6	—	—	—	24	—
5	7	—	—	—	35	—
6	4	—	—	—	24	—
7	2	1	50.0	1	14	7.2
>7	0	—	—	—	0	—
Totals	46	1		1	166	
Averages			2.2			0.6

All 3 cases occurring after gamma globulin were in this group; the attack rate was 1.6 (still less than a tenth of that among noninoculated persons). The efficacy of gamma globulin in the control of hepatitis in household contacts is again demonstrated.

These data corroborate the findings of others[2-5] who have used globulin for control of infectious hepatitis in presumably susceptible contacts.

FAMILY SIZE IN RELATION TO INCIDENCE OF SECONDARY CASES

Ipsen[6] found that secondary attack rates increased with family size.

The effect of family size on secondary case incidence was next investigated in the 235 families

history of hepatitis was the only criterion for immunity. The greatest number of families with secondary cases were those with 3 to 6 susceptible members, but the greatest number of secondary cases and the highest rate per 100 susceptible persons occurred in families with 7 susceptible members (38.1 per cent).

Since the infection rate after inoculation was approximately a tenth of that in unprotected persons in this series, the families in which gamma globulin was used were separated from those in which it was not used, to determine the effect of family size on secondary attack rate among family contacts (Table 4).

In 151 families, with 616 susceptible members, no gamma globulin was given, and an additional 17

families, with 86 susceptible members, received inoculation after 1 or more secondary cases had developed. These were added to those who had not received gamma globulin and considered as occurring before inoculation. In these 168 families 111 secondary cases among 702 susceptible contacts occurred, giving a secondary attack rate of 15.8. No cases of hepatitis occurred in these families after inoculation.

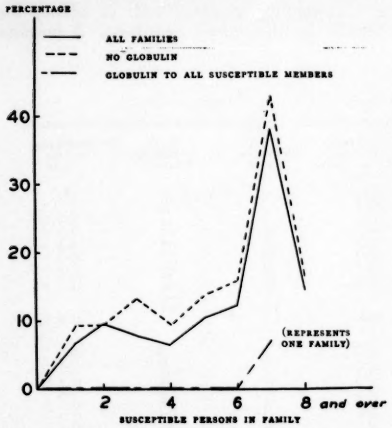


FIGURE 2. *Incidence of Secondary Attacks in Relation to Family Size.*

There were 21 other families in which gamma globulin was given to only a portion of the susceptible members. Among these 4 cases subsequently occurred, 2 in persons not protected and 2, thirty-five and thirty-six days, respectively, after administration of gamma globulin, both being mild cases. All these cases occurred in separate families containing 2, 4, 5 and 7 susceptible members. No family in which globulin was given to 1 or more susceptible contacts had more than 1 secondary case, in contrast to 22 unprotected families, which had 2 to 7 secondary cases.

In 46 families all 166 susceptible members were given globulin shortly after the onset of the initial case. Among these only 1 secondary case developed; this occurred thirty-five days after administration of gamma globulin in a family with 7 susceptible members. The secondary attack rate for household contacts in these protected families was 0.61 per cent.

The families with the highest attack rate among the 46 receiving and the 168 not receiving gamma globulin were those with 7 susceptible family contacts. There was a striking difference, however, in these rates: for the unprotected families the rate was 42.9 per cent, in contrast to one of 7.2 per cent in the protected families (Fig. 2).

Only 4 cases occurred among the 21 families in which only 46 out of 91 susceptible members were inoculated. Two of these were in uninoculated persons; the other 2 cases occurred in persons who had received gamma globulin thirty-six days before the onset of the disease. Although the numbers are too small to be significant, it can probably be said that partial protection of susceptible contacts cut down the secondary attack rate, which was only 4.3 per cent, with secondary cases in only 19.0 per cent of the families.

The percentage of families in each size with secondary cases increased in proportion to family size, both in the total 235 families and in the 168 unprotected families (Fig. 3). This is similar to Ipsen's[6] findings. Crowding, therefore, can be said to be a factor in the spread of infectious hepatitis. A common source of infection, whether respiratory or enteric, within the household will have an opportunity to affect a greater number in families with many than in those with few susceptible members. Increasing secondary attack rates with increasing family size is not, therefore, an argument for the respiratory tract as the only mode of transmission.

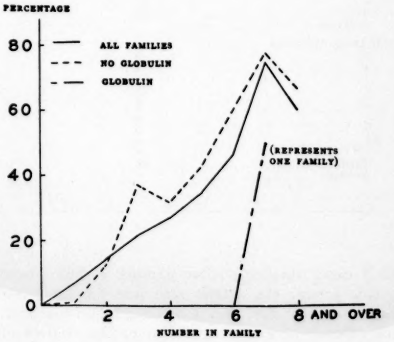


FIGURE 3. *Comparate Rates of Secondary Attacks in Protected and Unprotected Families.*

The efficacy of gamma globulin in the control of infectious hepatitis is eloquently shown by the marked difference in the attack rates of protected and unprotected families. Even in vulnerable families of 7 susceptible contacts the rate was six times higher in unprotected families.

Conclusions

Serum globulin was effective in reducing the incidence of secondary cases among family contacts of patients with infectious hepatitis. The secondary attack rate in families receiving no inoculation was 15.2 per cent. That in families protected by globulin was 0.6 per cent.

Family size was also a factor influencing the secondary attack rate.

The highest over-all attack rate (primary and secondary) occurred in children of school age in the general population and in the 235 families studied; schools were often cited as probable sources of infection.

I am indebted to Drs. Theodore H. Ingalls and Johannes Ipsen for their helpful suggestions in the preparation of this paper.

References

1. Bennett, A. M., et al. Endemic infectious hepatitis in infants' orphanage. II. Epidemiologic studies in infants and small children. *Arch. Int. Med.* **90**:37-53, 1952.
2. Brooks, B. F., Hsia, D. Y.-Y., and Gellis, S. Family outbreaks of infectious hepatitis: prophylactic use of gamma globulin. *New Eng. J. Med.* **249**:58-60, 1953.
3. Lilienfeld, A. M., Bross, I. D. J., and Sartwell, P. E. Observations on outbreak of infectious hepatitis in Baltimore during 1951. *Am. J. Pub. Health* **43**:1085-1096, 1953.
4. Stokes, J., Jr. Epidemiology of viral hepatitis A. *Am. J. Pub. Health* **43**:1097-1100, 1953.
5. Stokes, J., Jr., et al. Infectious hepatitis: length of protection by immune serum globulin (gamma globulin) during epidemics. *J. A. M. A.* **147**:714-719, 1951.
6. Ipsen, J., Donovan, W. R., and James, G. Sociologic factors in spread of epidemic hepatitis in rural school district. *J. Hyg.* **50**: 457-470, 1952.

GAMMA GLOBULIN IN THE PREVENTION OF INFECTIOUS HEPATITIS*

Studies on the Use of Small Doses in Family Outbreaks

David Yi-Yung Hsia, M.D.,† Maurice Lonsway, Jr., M.D.,‡ and Sydney S. Gellis, M.D.§

BOSTON

ALTHOUGH the value of gamma globulin in the prevention of infectious hepatitis has repeatedly been shown[1-6] the minimal effective dose remains to be determined. The increased demand for gamma globulin as a result of its use in the modification and prevention of poliomyelitis[7-10] has made it essential to conserve this material whenever possible. The present paper concerns the use of small doses of gamma globulin in preventing the spread of infectious hepatitis in family outbreaks. Its use in institutional outbreaks will be discussed later.[11]

Stokes and Neefe[1] first demonstrated the value of gamma globulin prepared from pooled human plasma in the prevention of infectious hepatitis by administering 0.15 cc. per pound of body weight to a group of campers involved in an outbreak of the disease. The effectiveness of gamma globulin was also noted in epidemics involving the personnel and inmates of institutions[2, 3] and large numbers of military personnel in World War II,[4] 0.06 to 0.12 cc. per pound of body weight being used. Recently, Stokes[5] suggested that as little as 0.01 cc. per pound of body weight may be protective against infectious hepatitis.

In studies on family outbreaks of infectious hepatitis, Brooks, Hsia and Gellis[6] found a high incidence of secondary cases after an initial sporadic case within the family. Secondary cases appeared in 48 per cent of 29 families in which gamma globulin was not administered to the contacts. Among these, hepatitis with jaundice subsequently occurred in 18 of 51 exposed children. In contrast only 1 case of infectious hepatitis developed among the 33 adults and 22 children who were exposed but who had been given 0.1 cc. of gamma globulin per pound of body weight.

The present report represents a continuation of the initial study on family outbreaks of infectious hepatitis using a smaller dosage of gamma globulin.

Methods and Materials

All the families included in this study were seen in the Children's Medical Center from January to July, 1953. The criteria for diagnosis in the initial case in each family were the same as those previously presented.[6] In addition to the clinical diagnosis the condition was confirmed in each case by positive liver-function tests. None of the patients had received injections or transfusions within six months of the onset of symptoms.

After the initial case had been diagnosed, alternate members of the family were given 0.01 cc. of gamma globulin¶ per pound of body weight. The remaining members of the family served as controls. For selection to be completely unbiased the youngest member of each even-numbered family in the order of appearance in the clinic was designated to receive gamma globulin. The second youngest member of that family was designated as a control,

*From the Medical Service, Children's Medical Center, the Department of Pediatrics, Beth Israel Hospital, and the Department of Pediatrics, Harvard Medical School.
Aided by grants from the Playtex Park Research Institute and the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.
†Instructor in pediatrics, Harvard Medical School; assistant physician, Children's Medical Center; associate physician, Beth Israel Hospital.
‡Fellow in pediatrics, Out-Patient Department, Children's Medical Center.
§Assistant professor of pediatrics, Harvard Medical School; physician, Children's Medical Center; pediatrician-in-chief, Beth Israel Hospital.

¶Kindly supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

the third youngest received gamma globulin and so forth. In all odd-numbered families the youngest member was designated as a control, the second youngest received gamma globulin, the third youngest served as a control and so forth.

None of the patients included in this study required hospitalization so that all other members of the families were theoretically exposed. All families were studied for at least three months after the occurrence of the initial case. All secondary cases were diagnosed solely on the development of clinical jaundice, which was confirmed by serum bilirubin determinations.

Results

A total of 54 cases of infectious hepatitis occurred among the 40 families. The secondary cases are shown in Figure 1. All the exposed contacts who received gamma globulin are shown above the midline, and all the exposed contacts who received no gamma globulin and were designated as controls are shown below the midline.

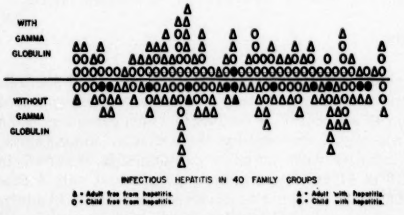

WITH GAMMA GLOBULIN
WITHOUT GAMMA GLOBULIN
INFECTIOUS HEPATITIS IN 40 FAMILY GROUPS
Δ = Adult free from hepatitis.
O = Child free from hepatitis.
Δ = Adult with hepatitis.
O = Child with hepatitis.

FIGURE 1. *Incidence of Secondary Cases in Families Followed after the Appearance of the Initial Case of Hepatitis.*

The alternate members of the family receiving 0.01 cc. per pound of body weight of gamma globulin are shown above the midline. The other members, acting as controls, are shown below the midline. All patients below fifteen years of age were classified as children. (The patient with hepatitis in the group receiving gamma globulin contracted the disease six days after receiving the material.)

Table 1 shows that in the untreated members of the families 2 of 55 exposed adults (4 per cent) and 11 of 40 exposed children (27 per cent) contracted hepatitis after the initial case had appeared in the home. In contrast none of the exposed adults and only 1 of the 57 exposed children receiving gamma globulin subsequently contracted hepatitis — in this case jaundice developed six days after gamma globulin had been given.

Discussion

The results from this new group of families confirms our previous finding that the exposure of children to hepatitis within family groups results in a surprisingly high incidence of secondary cases.[6] The attack rate of 27 per cent among untreated children in this series compares with one of 35 per cent in the previous series. It is of interest that the administration of gamma globulin to half the exposed adults and children in the families did not materially reduce the incidence of the disease among the untreated children.

The data demonstrate that the administration of 0.01 cc. per pound of body weight was highly effective in preventing the spread of infectious hepatitis among exposed adults and children within the family. Only 1 patient among 95 adults and children receiving this amount of gamma globulin contracted hepatitis, and in that case jaundice appeared only six days after injection. This dosage appears to be as effective as the 0.1 cc. per pound of body weight previously reported.[6] Since gamma globulin given in a dose of 0.005 cc. per pound of body weight did not appear to be completely effective in an institutional outbreak,[11] 0.01 cc. appears to represent the dosage of choice at present.

TABLE 1. *Incidence of Infectious Hepatitis among Exposed Adults and Children.*

GROUP	PERSONS NOT GIVEN GAMMA GLOBULIN		PERSONS GIVEN GAMMA GLOBULIN	
	NO. EXPOSED	CASES OF HEPATITIS	NO. EXPOSED	CASES OF HEPATITIS
Adults	55	2 (4%)	38	0
Children (under 15)	40	11 (27%)	57	1* (2%)
Totals	95	13 (14%)	95	1* (1%)

*Hepatitis developed 6 days after administration of gamma globulin.

Unfortunately, the data in this study are inadequate to show whether the protective effect of small dosages of gamma globulin against infectious hepatitis is due solely to passive immunity during the period of exposure or whether, as the passive immunity conferred by gamma globulin wanes, a mild unapparent infection occurs without clinical symptoms, conferring a lasting immunity. The latter mechanism has been suggested in studies conducted in the course of institutional outbreaks.[5] One may speculate whether the degree of exposure in the home is not as prolonged as that in an institution, where the disease is frequently endemic. If so, the requirements necessary for the development of passive and active immunity would be more difficult to obtain, and a purely passive effect from gamma globulin appears more likely to be responsible for the prevention.

Summary and Conclusion

Gamma globulin in a dosage of 0.01 cc. per pound of body weight was given to alternate members of 40 families, in each of which a sporadic case of infectious hepatitis had developed.

Only 1 case of hepatitis occurred among 38 exposed adults and 57 exposed children who were given gamma globulin. Jaundice was noted six days after injection in that case.

In comparison, secondary cases appeared in 2 of the 55 exposed adults (4 per cent) and 11 of 40 exposed children (27 per cent) who were the untreated controls within the same families.

Administration of 0.01 cc. per pound of body weight appears to be as effective as that of 0.1 cc. in preventing the spread of infectious hepatitis within family groups.

References

1. Stokes, J., Jr., and Neefe, J. R. Prevention and attenuation of infectious hepatitis by gamma globulin: preliminary note. *J. A. M. A.* **127**:144, 1945.
2. Havens, W. P., Jr., and Paul, J. R. Prevention of infectious hepatitis with gamma globulin. *J. A. M. A.* **129**:270-272, 1945.
3. Capps, R. B., Bennett, A. M., and Stokes, J., Jr. Endemic infectious hepatitis in infants' orphanage. I. Epidemiologic studies in student nurses. *Arch. Int. Med.* **89**:6-23, 1952.
4. Gellis, S. S., et al. Use of human immune serum globulin (gamma globulin) in infectious epidemic hepatitis in Mediterranean theatre of operations. I. Studies on prophylaxis in two epidemics of infectious hepatitis. *J. A. M. A.* **128**:1062, 1945.
5. Stokes, J., Jr., et al. Infectious hepatitis: length of protection by immune serum globulin (gamma globulin) during epidemics. *J. A. M. A.* **147**:714-719, 1951.
6. Brooks, B. F., Hsia, D. Y. Y., and Gellis, S. S. Family outbreaks of infectious hepatitis: prophylactic use of gamma globulin. *New Eng. J. Med.* **249**:58-60, 1953.
7. Hammon, W. McD., Coriell, L. L., and Stokes, J., Jr. Evaluation of Red Cross gamma globulin as prophylactic agent for poliomyelitis. 1. Plan of controlled field tests and results of 1951 pilot study in Utah. *J. A. M. A.* **150**:739-749, 1952.
8. *Idem.* Evaluation of Red Cross gamma globulin as prophylactic agent for poliomyelitis. 2. Conduct and early follow-up of 1952 Texas and Iowa-Nebraska studies. *J. A. M. A.* **150**:750-756, 1952.
9. Hammon, W. McD., Coriell, L. L., Wehrle, P. F., Klimt, C. R., and Stokes, J., Jr. Evaluation of Red Cross gamma globulin as prophylactic agent for poliomyelitis. 3. Preliminary report of results based on clinical diagnoses. *J. A. M. A.* **150**:757-760, 1952.
10. Hammon, W. McD., Coriell, L. L., Wehrle, P. F., and Stokes, J., Jr. Evaluation of Red Cross gamma globulin as prophylactic agent for poliomyelitis. 4. Final report of results based on clinical diagnoses. *J. A. M. A.* **151**:1272-1285, 1953.
11. Holzer, H., Martin, E., Gellis, S. S., and Hsia, D. Y.-Y. Unpublished data.

MEDICAL PROGRESS

TREATMENT OF BACTERIAL ENDOCARDITIS (Concluded)*

Maxwell Finland, M.D.†

BOSTON

Oxytetracycline. Reports of therapy with oxytetracycline in 27 collected cases of bacterial endocarditis[75, 113, 134, 136, 154, 164, 169-172, 174-178] indicate that the results were qualitatively similar to those obtained with chlortetracycline and equally difficult to evaluate (a few of these patients who were also treated with the latter antibiotic have been included among the cases treated with that agent). Although comparisons with the small numbers of cases involved are not warranted the results appear to be quantitatively slightly less favorable, for only 7 of these 29 patients achieved a favorable result and cure during the course of treatment with oxytetracycline (27 per cent recoveries from oxytetracycline, as compared with 36 per cent from chlortetracycline, the difference not being highly significant). Dosages and untoward effects were somewhat similar, but intravenous therapy with oxytetracycline was less frequently used, and at least 2 of the unfavorable results were due in large measure to gastrointestinal toxicity severe enough to warrant discontinuance of therapy.[170, 176] Moreover, although a good result was reported in 7 of the cases, the cure could be definitely attributable to the antibiotic in only 3: 1 due to a strain of bacteroides,[178] another to *Staph. aureus*,[175] and a third to *Str. viridans*.[177] In 2 of the remaining cases (1 due to *Staph. albus*[113] and the other to a strain of hemophilus[134]) streptomycin was used in combination with oxytetracycline; in a third (an infection with *Str. viridans*) the cure may already have been achieved by penicillin before the oxytetracycline was given,[177] and the fourth patient, whose blood cultures were negative throughout, was apparently cured by the combination of oxytetracycline and cortisone after oxytetracycline alone was considered to have failed.[172]

The causative organisms in the 19 failures were as follows: enterococcus in 6, *Str. viridans* in 7, *Staph. aureus* in 3 and *Esch. coli* in 2; in 1 patient the blood cultures were all negative. It is of interest that 6 of these patients received streptomycin along with the oxytetracycline during the course that failed. In 4 of these 6 patients cures were subsequently obtained by one or two courses of treatment with large doses of penicillin combined with streptomycin.[134] Cures were also obtained in 8 additional patients after the failure of oxytetracycline: in 3 by the administration of large doses of penicillin[134, 136, 176] and in 1 each with chlortetracycline given intravenously,[176] the combination of penicillin, probenecid and bacitracin,[154] penicillin combined with chloramphenicol,[75] the combined use of small doses of each of 5 antibiotics (including oxytetracycline) and a sulfonamide[171] and, in a patient who had only negative blood cultures, cortisone alone.[172]

The relation between the sensitivity of the infecting organism and the success of treatment is difficult to evaluate. Quantitative results of sensitivity tests in 5 cured patients showed the causative organism to be inhibited by 2.0 microgm. per cubic centimeter or less in 4, whereas 1 (a strain of *Staph. albus*) required 20 microgm. per cubic centimeter to inhibit, the cure being achieved

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

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†Associate professor of medicine, Harvard Medical School; chief, Fourth Medical Service, and associate director, Thorndike Memorial Laboratory, Boston City Hospital.

with the combination of oxytetracycline and streptomycin.[113] Of 11 patients in whom oxytetracycline failed, the organism was sensitive to 2.0 microgm. per cubic centimeter or less in 9, whereas the other 2 required 3.1 microgm. per cubic centimeter for inhibition. Fourfold or greater increases in resistance were recorded in 3 patients during oxytetracycline therapy,[134, 178] and in a fourth patient the minimum inhibiting concentration for a staphylococcus apparently increased from 0.25 microgm. to 2.5 microgm. per cubic centimeter during a course of chlortetracycline given before oxytetracycline therapy was started.[164]

Little can be deduced from these data beyond the fact that oxytetracycline is occasionally effective in cases of bacterial endocarditis. The evidence for any synergistic action with streptomycin in vivo is not borne out in these cases except possibly in 1.[113] The data, however, are too few to permit any far-reaching conclusions. Possibly, adequate dosage could not be achieved in most of the patients with failure, although some of them received intravenous supplements to the oral doses. The mechanism of action of oxytetracycline and the reasons for the failures are probably the same as those for chlortetracycline, which it closely resembles chemically.[179] It is also well to bear in mind that marked cross-resistance between the two antibiotics has been demonstrated in vitro,[180] and this seems to have developed in 1 of the cases mentioned above.[164]

Chloramphenicol. What has been said about oxytetracycline and chlortetracycline is true also of chloramphenicol, except that toxic effects are not prominent, intravenous administration has not been used, and even fewer reports are available for evaluation. Of 13 reported cases[75, 98, 111, 150, 164, 169, 171, 181, 182] cures are recorded in 5: 3 due to *Str. viridans*, 1 to *Staph. aureus*, and 1 in which only negative blood cultures were obtained. In 1 of the cured cases of endocarditis due to *Str. viridans* penicillin was also given and in vitro studies suggested that there was a synergistic action of the two antibiotics on the organism in that case.[75*] There were 8 failures, 3 in cases due to *Str. viridans* and *Str. faecalis* and 2 in cases caused by *Staph. aureus*. In 1 of the cases of staphylococcal endocarditis, penicillin was used; in the other chlortetracycline was given in addition to the chloramphenicol, cure apparently being achieved by combined treatment with penicillin, bacitracin and chlortetracycline.[150] Cures were also obtained after the failure of chloramphenicol in 2 of the patients[95, 169] with endocarditis due to *Str. viridans* by the use of large doses of penicillin, fortified in 1 case with probenecid by mouth.[95] Similarly, a cure was subsequently obtained in 1 of the cases of endocarditis due to *Str. faecalis* (already mentioned twice previously) by treatment with five antibiotics (including chloramphenicol) and a sulfonamide.

The clinical results in many of the present cases did not appear to correlate with the in vitro sensitivity of the infecting strains to chloramphenicol, and, in general, the minimum inhibiting concentrations were greater for this antibiotic than for chlortetracycline or oxytetracycline. Three of 4 strains in cured cases tested were sensitive to 2.5, 6.5 and 25 microgm. per cubic centimeter, and the other was reported as "highly sensitive," whereas of 6 strains in cases in which chloramphenicol failed, 1 was inhibited by 1.0, 2 by 2.5, 1 by 5.0, 2 by 10, and 1 by 12.5 microgm. per cubic centimeter. In the cured case, in which a strain of *Str. viridans* was inhibited by 6.25 microgm. of chloramphenicol per cubic centimeter, the organism was also inhibited by 0.2 units of penicillin alone but it was completely inhibited by the combination of 0.02 microgm. of chloramphenicol and 0.02 units of penicillin per cubic centimeter; the patient, who had failed to respond favorably to large doses of penicillin alone, was cured when smaller doses of that antibiotic were combined with chloramphenicol.[75]

The deductions that can be made from these results are similar to those already noted for chlortetracycline and oxytetracycline. A variable but relatively small proportion of cases of bacterial endocarditis appear to have been favorably affected by treatment with each of the three broad-spectrum antibiotics. The results of treatment with these agents are far less impressive than those achieved with the use of large doses of penicillin, either alone or particularly when combined with streptomycin. However, at least in some of the cured cases, especially some of those cured with chlortetracycline, the favorable results were obtained after apparent failures with these agents used alone or in combination. With chloramphenicol, as with each of the other two broad-spectrum antibiotics, apparently favorable clinical effects and failure to obtain positive blood cultures were noted in some patients during the administration of the agent, but clinical and bacteriologic relapses occurred either during the continued therapy or soon after discontinuance of the antibiotic. In a fairly large proportion of cases in which treatment with each of the broad-spectrum antibiotics had failed cures were subsequently obtained by the use of other antibiotics singly or in combination, and this was most frequently achieved with the combination of large doses of penicillin with streptomycin.

The extent to which specific antibiotic antagonisms may have been responsible for any of the failures or synergistic actions for the successes cannot be evaluated from these cases. These factors

*In an additional case due to *Str. viridans*, bacteremia persisted during treatment with penicillin alone and chlortetracycline alone, and a cure was subsequently achieved with the combination of oxytetracycline and chloramphenicol.[182]

may well have been important in some of the cases. It is also difficult to make any specific recommendations on the basis of such varied results beyond the obvious one that the sensitivity of infecting strains in cases of bacterial endocarditis must be tested, preferably with combined drugs that one contemplates using, as well as with the individual antibiotics. It remains to be seen, however, whether the results of in vitro tests for sensitivity will correlate better with clinical results after the accumulation of a much larger number of properly documented cases. It may also be concluded that, for initial therapy in any doubtful cases of bacterial endocarditis, or for treatment of any such cases in which one is impelled to begin the medication before the results of cultures and sensitivity tests become available, the use of large doses of penicillin supplemented with moderate doses of streptomycin, and not the administration of any of the broad-spectrum antibiotics, can be recommended as the therapy of choice.

Erythromycin and carbomycin. These agents, each of which has an antibacterial spectrum similar to that of penicillin, have only recently become available, and only limited numbers of cases of bacterial endocarditis treated with them have been reported.[184-189] Results recorded have been almost uniformly unfavorable although practically the maximum tolerated dose that can be given orally was used in all these cases.

With erythromycin only 1 recovery was recorded and that was in a case of endocarditis due to *Str. salivarius*,[184] whereas failures are reported in 6 cases, 3 due to *Staph. aureus*,[185, 186, 188] 2 to *Str. viridans*[184, 187] and 1 to *Str. faecalis*.[184] The organisms isolated before the erythromycin therapy was started were highly sensitive in vitro in every case; in the cured case it was inhibited by 0.05 microgm. and in the others by 0.4 or 0.8 microgm. per cubic centimeter. Except for a case due to *Str. salivarius*, all the failures were associated with marked increases in resistance of the infecting organism to erythromycin after relatively brief courses of treatment with this agent.

The only report of the use of carbomycin for the treatment of bacterial endocarditis is that of Hewitt and Wood,[189] and the only favorable effect that these authors observed was the temporary clinical improvement and control of bacteremia in a patient with staphylococcal endocarditis who died on the fifth day of treatment. In 5 other cases—2 due to enterococcus, 2 to nonhemolytic streptococci and 1 to *Staph. aureus* — the infections were totally unaffected by oral treatment, supplemented in some cases by intravenous injections of carbomycin. The organisms in all 6 cases were highly sensitive to small concentrations of carbomycin in vitro (0.16 to 1.6 microgm. per cubic centimeter), and resistance was not observed in the only patient in whom the organism was studied after therapy. Cures were subsequently achieved after the failure of carbomycin in 3 of these patients; in 1 of the cases of enterococcal endocarditis cure was obtained by treatment with penicillin and streptomycin, and both the cases of endocarditis caused by nonhemolytic streptococci were subsequently cured by large doses of penicillin alone.

From these meager reports it appears reasonable to conclude that these agents, at least by themselves, are not to be recommended for the treatment of endocarditis even when the infecting organism appears to be highly sensitive to them in vitro. Whether treatment with either of these agents will prove successful when it is combined with the simultaneous use of other antibiotics to which the infecting organism is also sensitive remains to be seen. In vitro studies carried out in this laboratory[190] suggest that the emergence of resistance to erythromycin may be depressed, delayed or in some cases even prevented by the use of such combinations of antibiotics, but this has not yet been confirmed in vivo. Indeed, marked increases in resistance of staphylococci to erythromycin have already been noted in 2 cases of bacterial endocarditis during combined treatment with erythromycin and streptomycin.[185]

Patients with Negative Blood Cultures

The problem presented by patients who have a clinical diagnosis of bacterial endocarditis and negative blood cultures is a highly important one. In the first place there is a striking difference in recovery rate after antibiotic treatment between patients with negative and those with positive cultures. Thus, among all patients treated at Mount Sinai Hospital in New York City from the advent of penicillin to June, 1949, there were 114 patients with positive and 26 with consistently negative blood cultures; 77.2 per cent of the former and only 38.5 per cent of the latter recovered.[191] In the cases collected by Cates and Christie[55] from the Medical Research Council's collaborative study in Great Britain the difference was even more striking: 52 per cent of 408 patients with positive blood cultures recovered, whereas only 18 per cent of 34 patients with negative blood cultures eventually survived treatment with penicillin and recovered. In both series the diagnosis in a large proportion of the fatal cases with negative blood cultures was verified at autopsy; in the British cases it is also stated that the post-mortem findings were similar in every way to those in patients in whom the blood cultures during life were positive and who died after treatment. Heart failure, however, was almost three times as frequent among the patients with negative (62 per cent) as among those with positive blood cultures (22 per cent) in the British cases.

Friedberg[191] ascribed some of the excess mortality to the fact that the absence of positive blood cul-

tures in some patients led to erroneous diagnoses and hence to failure to treat the patients for subacute bacterial endocarditis. In other cases the failure to obtain a bacteriologic diagnosis resulted in delay in treatment and, as might have been expected, in difficulties in determining the proper type of therapy as well as the proper dosage.

On the other hand it is highly probable that the same conditions that prevent the organisms within the lesion from getting into the blood stream contribute to the poor diffusion of the antibiotic into the vicinity of the organisms and thus may account for the poor results. Along these lines, Cates and Christie[58] noted that the response of the patients with negative blood cultures to treatment with penicillin was definitely unsatisfactory: of 19 patients, although the fever was controlled throughout the period of treatment, only 6 eventually survived. The authors suggested that the results might have been somewhat better if more intensive treatment such as that employed by Loewe and Eiber[122] had been used. Loewe and Eiber reported only 3 deaths in 11 patients with negative blood cultures; only 1 of their fatal cases gave evidence of active infection at post-mortem examination, the second patient died of cardiac failure and no organisms could be found on either microscopical or bacteriologic study at autopsy, and the third, who died of coronary occlusion nine months after the termination of treatment, was found to have healed bacterial endocarditis without any evidence of active infection.

The possible causes of failure to obtain positive blood cultures in patients with bacterial endocarditis have been enumerated by Bloomfield and Halpern[12]; they involve factors related to the manner in which organisms might gain egress from the lesion into the blood stream, the manner in which the host may dispose of the organisms once they get into the circulating blood, and also problems of bacteriologic technic involved in causing the bacteria to multiply in artificial mediums so that they can be recognized and identified. It should also be emphasized that recent and especially prolonged but inadequate therapy with penicillin or other antibiotics for the same or another illness may decrease the opportunity for obtaining positive blood cultures for long periods. This may result, in part, from the fact that the healing of endocardial lesions and vegetations advances to a further stage in patients who have been inadequately treated than in previously untreated patients,[47, 50, 81, 192] and this, in turn, causes greater sequestration of the organisms within fibrin and scar tissue so that they are less likely to reach the circulating blood. Under the category of bacteriologic technic the following causes of failure to obtain positive blood cultures may be mentioned: failure to keep the cultures under incubation and observation for long enough periods,[31] failure to use selective mediums that would support the growth of fastidious organisms, anaerobic bacteria or fungi,[193] and possibly the failure to obtain blood cultures at different times of the day and under varying circumstances.[194]

The obvious deduction that suggests itself from the observations on mortality is that treatment should not be delayed and that, for the purpose of initiating therapy, the results of the blood culture should be eliminated from the criteria for the diagnosis of subacute bacterial endocarditis; this has been suggested by Friedberg.[191] Such a deduction is obviously based on the expectancy that better results would be obtained if the delay in obtaining positive blood cultures were avoided. Long and well documented experience, however, would be required to determine definitely whether the mortality in patients with negative blood cultures who are treated promptly — that is, as soon as the clinical diagnosis is established — is really lower than that in similar cases in which treatment is delayed only until after the results of the blood culture are obtained, when the same criteria for the clinical diagnosis, severity, previous course and types of treatment are all taken into account. In the meantime it is necessary to weigh this hope against the possible advantages, if any, of waiting for the results of cultures. Available information, however, may be used as a basis for adopting the decision for early treatment.

There are a few data that indirectly throw some light on the significance of delaying treatment for the purpose of waiting for a positive blood culture. Griffith and Levinson,[88] reviewing their results in 140 patients with positive blood cultures, found that the culture was positive on the first day in 129 and on the second day in 8. In only 3 patients were positive cultures obtained on the third day or later, — 1 each on the third, fifth and fifty-sixth days, — and in the last of these, 78 previous cultures had been negative. In their series, therefore, less than 3 per cent of patients eventually showed positive blood cultures if they failed to yield such positive cultures for the first time during the first two days, and in less than 1 per cent was the first positive culture obtained from blood taken after the fifth day.

Considered from another point of view, the Medical Research Council series[58] included 3 recoveries among 11 cases in which less than 3 negative cultures were obtained before treatment was started, and there were also 3 recoveries among 20 patients in whom 3 to 10 negative cultures had been obtained. Presumably, the latter group represented the cases in which there was a longer waiting period for treatment to begin. The difference in mortality in these small groups may not be highly significant statistically, but it suggests that a higher recovery rate was obtained when there was less delay in obtaining a larger number of cultures. On the other hand, in the cases reported by Loewe and

Eiber,[122] in which the results were more favorable, the 2 patients who succumbed under treatment had 3 and 12 sterile blood cultures, respectively, and the others, in whom the treatment was more successful, had 5 to 20 negative blood cultures before treatment was started.

Some authors have attempted to correlate the end result with the estimated duration of illness before treatment was begun. Such data are not directly relevant to the problem of delaying treatment solely for the purpose of establishing a bacteriologic diagnosis, for they reflect primarily the effects of the delay that is due to the failure of the patient to seek proper medical attention; they are nevertheless of considerable interest. In the British series[55] the mortality increased with the duration of illness when treatment was begun, but this was related more to the fact that heart failure was more frequent among older patients. Correll and his co-workers[51] also noted that there was an increase in both mortality and disability among the recovered patients in relation to the duration at onset of treatment. In Friedberg's[101] series there were 88 per cent recoveries in patients treated less than two months after the onset of illness, as compared with 55 per cent in those who had been ill for more than two months when treatment was started. On the other hand, Dawson and Hunter[8] noted no definite relation of the outcome of treatment to the duration of illness, and Mokotoff and his associates[18] concluded from their cases that duration alone does not alter the results unless complications have already occurred.

From these data it appears that a brief delay in treatment should not seriously impair the end results in patients who do not already have serious complications that make the prognosis unfavorable. From the bacteriologic point of view, however, a delay of more than forty-eight hours, or at most five days, is logistically unsound and does not seem justified, provided that treatment is begun only after adequate samples of blood for culture have been obtained during this waiting period for later examination; only rarely would one expect to obtain positive results after two to five days of intensive efforts. This period seems to be a reasonable one for obtaining bacteriologic data that may subsequently be of great value in the conduct of therapy and yet have a minimum prospect of impairing the end result.

The value of obtaining a positive blood culture in any patient suspected of having bacterial endocarditis is generally conceded and is worth all the efforts that are put into the procedures necessary for obtaining optimum results. On the other hand it is highly and almost equally important not to subject patients with doubtful cases to the unnecessary hardship entailed in the arduous and costly procedures involved in the course of treatment.* Moreover, the initiation of treatment for bacterial endocarditis in patients who turn out to have other diseases may result in halting the efforts to establish the proper diagnosis and thus to institute the proper treatment which may be entirely different. Finally, it should be borne in mind that the data cited have dealt with cases in which a diagnosis of subacute bacterial endocarditis was made retrospectively. These data do not take into consideration the much larger number of patients in whom the diagnosis of subacute bacterial endocarditis was entertained and from among whom these patients had been selected.

The following procedures may be suggested for the management and therapy of subacute bacterial endocarditis in patients with negative blood cultures:

Major emphasis must be placed on the clinical criteria for diagnosis. It is therefore necessary to insist on fairly definitive criteria — namely, changing murmurs, embolism, petechiae, evidence of focal embolic nephritis and clubbing of the fingers in patients with known valvular disease or with congenital cardiac lesions. Parsons et al.[106] have also recently stressed the importance of unexplained anemia in patients with murmurs or unexplained fever, or both, in the diagnosis of bacterial endocarditis. Insistence on at least some of these major manifestations is essential to avoid subjecting many patients to the rigors of long confinement, discomfort and expense, to say nothing of the psychic trauma involved.

Multiple blood cultures must be performed during the first two to five days and opportunities must be taken to obtain such cultures in relation to special episodes such as chills, rises in temperature and the occurrence of new embolic phenomena or petechiae, and perhaps also after mild physical exercise. It is therefore best to obtain cultures on more than one occasion, up to four or more times each day. Under optimum conditions these cultures should include, in addition to the routine broth mediums ordinarily used, agar pour plates, special mediums that permit the growth of fastidious organisms, including anaerobes and fungi, incubation and observation of these cultures for as long as three weeks before they are discarded as negative, and cultures of aspirated sternal or iliac bone marrow, particularly in patients who are or have recently been under treatment with antibiotics, but there seems to be no advantage to including arterial as well as venous blood for culture. The last recommendation is based on a report by

*Dowling and Murray[126] calculated the cost of an average hospital stay of seventeen and four-tenths days for a private patient with bacterial endocarditis in metropolitan Washington, D. C., in 1948 to be $534.49. A rough estimate of present costs in large teaching hospitals, with the type and duration of treatment now recommended, would approximate three times that amount. These figures do not include the professional fees of the attending physician and consultants.

Mallén and his co-workers,[197] who obtained positive cultures of bone marrow in 5 patients with subacute bacterial endocarditis when venous blood obtained simultaneously was sterile; in 4 of these patients penicillin was being given at the time. On the other hand, although they obtained some positive results in cultures of venous blood when those of arterial blood drawn simultaneously were negative, the reverse was not encountered.

Treatment should be undertaken before the results of the blood culture are known — that is, treatment need not be delayed more than the two to five days during which the cultures are made. This period, of course, may be shortened for patients who have extensive emboli or who are already in moderate or marked congestive heart failure, but there seems little reason to undertake therapy even in such cases before at least twelve to twenty-four hours of intensive efforts to obtain proper bacteriologic data.

The treatment of these cases should then be vigorous and should be undertaken in a manner similar to that which would be used if the organism were known to be only moderately sensitive to penicillin. At present it is generally recommended that moderately large doses of penicillin be given at first; these doses should then be increased rapidly, and streptomycin also added if the initial treatment appears to be inadequate.[130, 135, 191, 198] A reasonable starting dose should be about 250,000 units every three hours given as the aqueous soluble penicillin G intramuscularly. This dose would be increased to 1,000,000 units every two or three hours, and streptomycin, 0.5 gm. every six or eight hours, would be added if a good response of the fever and symptoms were not obtained within the first week under the smaller dosage regimen or if, in the meantime, positive results of blood cultures become available suggesting that the treatment originally begun might have been inadequate. Probenecid, in oral doses of 2 to 4 gm. a day, may be used when the larger doses or frequent administrations cause excessive local irritation and are not well tolerated.

If a good response is obtained, treatment must be continued for six to eight weeks. The patient should then be observed and blood cultures taken at intervals depending on the response of the fever, leukocyte count and erythrocyte sedimentation rate. The leukocyte counts and erythrocyte sedimentation rates may provide the only guides to the response after the patient becomes afebrile since blood cultures are likely to continue to be sterile, and embolic phenomenon may continue to occur when treatment of the infection is optimum and even after the infection has been cured. The possibility of drug fever must always be considered when one is evaluating the course of the patient during treatment and may require the use of antihistaminics or alternate forms of drugs (penicillin O for penicillin G[199] or dihydrostreptomycin for streptomycin, and vice versa); even other antibiotics might be considered as alternative therapy, since, as already noted, some patients with negative blood cultures have been cured with each of the broad-spectrum antibiotics.

If such a course is adopted, the proportion of recoveries among patients treated for subacute bacterial endocarditis who have negative blood cultures may, of course, increase. Such an increase, however, may be the result of inclusion of patients who, under observation for somewhat longer periods, might have yielded positive blood cultures and thus been considered in that category; the results would, therefore, not necessarily be comparable to those previously reported. However, it is imperative that such cases be carefully studied and properly documented so that the accumulated experience may provide a firmer basis for a more rational approach to the problem.

The possibility of using ACTH or cortisone for the purpose of reducing the inflammatory and connective-tissue reaction locally in and around the vegetation and thus perhaps helping liberate the bacteria into the blood stream might be offered as a logical aid to a specific etiologic diagnosis. These hormones might even be suggested as an aid to the treatment of these cases by permitting better access of the drug to the organisms.[172] Their use might be particularly inviting in patients with evidence of active rheumatic fever in whom the diagnosis of bacterial endocarditis is suspected,[200-203] and this might then be considered as good treatment both for the rheumatic fever and for the possible endocarditis. There is little if any acceptable evidence in support of such suggestions.* At present the use of these agents is not to be recommended except as an experimental procedure under the most rigidly controlled conditions — certainly not without due consideration of the risks suggested by the large amount of evidence already accumulated that these hormones depress resistance to many infections in man and may actually reduce the effectiveness of antibiotics in certain infections.[204] Indeed, a number of cases have already been described in which bacterial endocarditis clearly developed during the course of prolonged treatment of acute rheumatic fever with ACTH and cortisone.[200, 202, 203]

Prophylaxis

The use of antibacterial agents, particularly penicillin, during dental extractions in susceptible persons (those with valvular or congenital heart disease) has been advocated by almost all writers

*Suzman,[204] however, obtained prompt and favorable clinical responses with cortisone therapy in 2 cases of subacute bacterial endocarditis that had failed to respond to massive doses of antibiotics; 1 patient was well six months after a twelve-week course, and in the other "suppression of the disease has been maintained satisfactorily on a small daily dose of cortisone for a period of 8 weeks."

concerned with the antibiotic therapy of subacute bacterial endocarditis.[14, 31, 63, 66, 206-208] It has also been recommended for routine use in patients in whom damage to the cardiac valve is present or suspected, in relation to certain other types of procedures and operations, including the antepartum and post-partum periods,[209, 210] the preoperative and postoperative periods of prostatectomies and other genitourinary operations and also during various types of diagnostic procedures and instrumentation.[57, 66, 166, 207, 211] Sulfonamides have been used in the past,[2] and chlortetracycline has also been suggested more recently in relation to operations and other procedures[66, 166, 211]; these appear to be preferable to penicillin in such situations because organisms of moderate or high resistance to penicillin are somewhat more frequent in the cases of endocarditis that follow such manipulations than those found in the cases that follow dental extractions.[166]

These recommendations may have a sound basis in principle and from a practical clinical point of view, but it is important to point out two important facts: the value of the procedure has never been proved, and the possible risks and dangers involved have never been evaluated. These points require some elaboration.

In the first place, there is as yet no valid proof that the application of prophylactic procedures according to any of the programs that have been thus far recommended has actually prevented the subsequent development of any significant number of cases of bacterial endocarditis. It is, of course, well known that the symptoms of bacterial endocarditis appear in a significant temporal relation to dental or other surgical manipulations in a large proportion of cases of bacterial endocarditis.[2, 15, 55, 208, 212, 213] Of interest in this connection is an observation made by Palmer and Kempf,[212] who took blood cultures in 82 patients with rheumatic heart disease before, immediately after and ten minutes after the extraction of one or two teeth under local anesthesia. All the pre-extraction cultures were negative, but positive cultures were obtained in 14 patients immediately after the extraction. In 13 of these the cultures taken ten minutes later were sterile, and these patients remained afebrile, but in 1 patient in whom a positive culture was obtained at that time fever later developed and the patient died.

Apart from such data, however, the only substantial evidence that has been advanced in support of the recommendations for chemoprophylaxis of bacterial endocarditis has been the reduction in the bacteremia in persons pretreated with sulfonamides[2, 208, 214-216] or with penicillin.[208, 216-219] It may be added that the strains of nonhemolytic streptococci cultured from the mouth and from areas of dental sepsis closely resemble those obtained from the blood of patients with subacute bacterial endocarditis.[2, 101, 212, 220]

Although these are important and well documented observations, they cannot be accepted as adequate proof of the value of the same prophylactic procedures in preventing the occurrence of bacterial endocarditis. Such proof would require the long-term follow-up study of large numbers of susceptible persons in whom similar dental procedures are carried out, in comparable cases, with and without prophylaxis, to obtain statistically valid comparisons. The numbers of cases required to validate the use of prophylaxis may be surmised from the observation of Kelson and White,[2] who calculated that the risk of having an attack of subacute bacterial endocarditis after any single tooth extraction in a susceptible patient with cardiac disease is approximately 1:533. No data in numbers of cases approaching the magnitude suggested by this figure have yet come forth.*

On the other hand, at least 4 cases have been reported in which the symptoms of the onset of an attack of subacute bacterial endocarditis, or of a relapse in a cured case, followed a tooth extraction that was carried out under chemoprophylaxis, the interval being short enough to suggest that it probably resulted from that episode.[25, 65, 111, 222] Penicillin had been used alone in 3 cases and together with sulfadiazine in a fourth. In 1 of these a single dose of 400,000 units of penicillin in oil and beeswax was given before the extraction[65]; in the second, full doses of sulfadiazine were used and supplemented by injections of 25,000 units of penicillin every three hours before and for two days after the extraction,[222] in the third 15,000-unit doses were given intramuscularly every three hours for fourteen hours before and sixty-four hours after the operation,[25] and in the fourth the patient received 6,000,000 units in six days and endocarditis due to a penicillin-resistant strain subsequently developed.[111]

The seriousness of the disease that one is attempting to prevent would warrant a certain amount of risk if the procedure recommended could be proved efficacious. What risks are actually involved in the use of prophylactic antibiotics, apart from the problems of untoward reactions and the possibilities of sensitization, have not been clearly defined and may be extremely difficult to quantitate. However, there is some evidence that significant changes take place in the flora of the mouth during the prophylactic use of penicillin or during treatment with moderate doses of penicillin, chlortetracycline or oxytetracycline in specific infections; these changes involve a moderate but probably significant increase in the resistance of the common alpha-hemolytic and nonhemolytic streptococci, as well as a rise in the number and proportion of gram-

*Extraction of all teeth has been suggested as useful prophylaxis of recurrences in subacute bacterial endocarditis on the basis of preliminary observations in only 7 cases in which this was carried out successfully.[221]

negative organisms and in the numbers and resistance of staphylococci.[223-227] The application of antibiotic prophylaxis, therefore, may result in a reduction in the relative number of organisms that are susceptible to the prophylactic agent but may also involve the definite possibility of an increase in the proportion and perhaps in the total numbers of those that are relatively or markedly resistant to that agent. If these organisms then invaded the blood stream and implanted themselves on a damaged valve, they could result in infection; this appears to have happened in at least one of the cases previously mentioned.[111]

These remarks should not be interpreted as indicating that a case against the use of antibiotic prophylaxis has been made. The frequency with which dental extractions, surgical procedures and diagnostic instrumentation are noted as antecedent events in cases of bacterial endocarditis is sufficient to warrant continuing such usage unless it can be shown to be ineffective or harmful.

However, from the practical point of view of the application of antibiotics for chemoprophylaxis, these remarks are meant to emphasize the fact that there are, at present, no data from which one could determine with any degree of assurance the following points: whether or not treatment before the actual time of dental manipulation or other surgical or diagnostic procedures is actually of any importance, and if it is, for how long before the procedures such prophylaxis should be applied; the optimum agent or agents, even for any given type of operation or procedure; the proper dosage of these agents for prophylaxis; and the optimum duration of administration for prophylactic purposes. These remarks have also been meant to call attention to the great need for the realization that such a procedure is not without certain risks and that data are not yet available, but are urgently needed, from which these risks could be measured and compared with any potential benefit that may be derived from the prophylactic uses of antibiotics. Indirectly, they suggest that there may be a profitable area of exploration for prophylaxis with agents or measures other than the use of the antibiotics on which one must depend for the definitive treatment of the infection that one is attempting to prevent.

Miscellaneous Surgical and Obstetric Aspects

As stated at the outset, no attempt has been made to present a complete or well rounded review of all the problems concerned with the therapy of bacterial endocarditis, or even of the phases that concern the use of antibiotics in this disease. Only some aspects of current and general interest and others of particular personal interest were chosen for discussion. A few additional subjects that may bear directly on the cure of the infection and on the end-results in certain cases are briefly mentioned.

The highly successful results of the surgical closure of patent ductus arteriosus[228-231] offer a prophylactic measure of first magnitude for both initial attacks and for recurrences of bacterial endocarditis in patients with this congenital anomaly; this procedure may also be a major factor in the cure of active cases of endocarditis in such patients.[206, 228-232] The same antibiotic treatment that is indicated for the infecting organism is usually recommended and carried out before the surgical operations are undertaken in cases of patent ductus arteriosus complicated by bacterial endocarditis, and the operation may be successfully performed during the course of the therapy for the subacute bacterial endocarditis.[16, 36, 37, 168, 230] However, recoveries from the surgical procedure alone without the use of chemotherapy or antibiotics have been recorded.[206, 228-232] Indeed, patients have been cured by the operation after failure of the antibiotic treatment alone. Surgical treatment is therefore indicated for patent ductus arteriosus even after the patients have been cured of bacterial endocarditis.[6, 228-231] Recurrent infection in these cases is rare but may follow the operation.[22, 40, 233]

The rupture of an infarcted and infected spleen and persistence of infection in splenic abscesses even after apparent bacteriologic cure of the endocardial lesion has been attained have been recorded as a cause of death or as a contributing factor in the failure of therapy in a number of patients.[10, 27, 31, 46, 55, 71, 110, 169, 173, 234, 235] The observations in such cases suggest that when a diagnosis of a splenic abscess is made or suspected in a patient under treatment or after therapy for bacterial endocarditis, splenectomy may be a useful and even life-saving procedure. The success of this operation will, of course, depend on many other factors, particularly on the presence of other large embolic areas with infection.

Embolectomy and excision or ligation of infected arteriovenous fistulas or of accessible mycotic aneurysms during the treatment with antibiotics offer additional surgical procedures that may be helpful in increasing the number of permanent cures in certain types of apparently resistant or recurrent infections.[40, 236-241]

Finally, attention may be called to the remarkable successes that have been achieved in cases of bacterial endocarditis complicating pregnancy and the puerperium.[13, 23, 55, 209, 210, 242-245] Treatment of the active infection during the course of pregnancy has proved successful in as great a proportion of cases as in nonpregnant patients of the same age group and cardiac status. Proper and adequate therapy has resulted not only in cures of the mothers but also in successful deliveries of live and healthy children in the great majority of cases. It thus appears from the reports of a number of observers[13, 23, 55, 209, 242, 243] and also from a recent survey by Pedowitz and Hellman[210] that, with the modern

management of pregnant cardiac patients in heart failure, those with bacterial endocarditis appear to tolerate the pregnancy as well as those who do not have this infection. There thus appear to be few if any special indications for therapeutic abortions in any of these cases, and the type of delivery selected should be dictated by obstetric rather than cardiac considerations.

Summary and Conclusions

The literature dealing with selected aspects of the antibiotic therapy of bacterial endocarditis is critically reviewed. Penicillin is still regarded as the most important single agent for this disease. The optimum method presently available for administering penicillin in this disease is considered to be the use of large and frequent intramuscular injections of the soluble sodium or potassium salt of penicillin G, supplemented, when necessary, by the use of probenecid.

The results of the use of antibiotics other than penicillin in the treatment of bacterial endocarditis are summarized. Streptomycin appears to be the most valuable of those currently available; although it has proved effective when used alone in the treatment of some cases of infection with susceptible organisms, the best results have been obtained in combination with large doses of penicillin in the treatment of cases due to organisms that are only moderately or slightly sensitive to either or both of these agents.

Bacitracin also appears to have been highly successful in the treatment of a small number of cases of bacterial endocarditis due to gram-positive organisms in which it was given in doses of about 100,000 units daily in combination with large doses of penicillin; further trials of such therapy appear to be indicated in cases in which the organism is not highly sensitive to penicillin alone.

Each of the broad-spectrum antibiotics, chlortetracycline, oxytetracycline and chloramphenicol, appears to have been responsible for cures in a minority of the cases in which it has been used, but the over-all results have not been nearly so impressive as with penicillin and streptomycin and their role in the cure of many of the cases is difficult to assess. In individual cases, however, each of these agents, particularly chlortetracycline, has proved to be life saving.

Erythromycin and carbomycin have been used in only a few cases, but almost uniformly without success. Most of the cases of failure with erythromycin alone were associated with a rapid and marked increase in resistance of the infecting organism during therapy.

Although there appears to be a good correlation between the sensitivity of the causative organisms to penicillin or streptomycin and the results of therapy with these agents, most of the failures with the broad-spectrum antibiotics and all the failures of treatment with erythromycin and carbomycin occurred in patients in whom the infecting strain was moderately or highly sensitive to the antibiotic given at least before treatment was begun.

The need for critical evaluation of the antibiotic prophylaxis of bacterial endocarditis is stressed.

Finally, attention is called to the favorable results obtained from surgical treatment in cases of patent ductus arteriosus or of mycotic or arteriovenous aneurysms. The possible usefulness of splenectomy in selected cases is suggested. The highly favorable results obtained in bacterial endocarditis complicating pregnancy and the puerperium are also noted.

The report on probenecid by the Council on Pharmacy and Chemistry[88] states: "*Salicylates should not be administered in conjunction with probenecid because the therapeutic actions of the two drugs are antagonistic.*" This statement applies to this combination only in the treatment of gout, in which the uricosuric actions of the drugs negate each other. In rheumatic fever, however, there appear to be neither antagonistic nor enhancing effects. Dr. William P. Boger, in a personal communication on October 2, 1953, informed me that probenecid does not affect the blood levels of salicylates but still exerts its enhancement effect on penicillin in the presence of high salicylate levels. Probenecid, therefore, may properly be used with salicylates in patients who, while under treatment with penicillin for subacute bacterial endocarditis, are also suspected of having active rheumatic fever.

Regarding short-term therapy and the use of repository penicillin preparations, Geraci and Martin[346] reported on 23 consecutive patients with penicillin-sensitive streptococcal endocarditis treated with a combination of penicillin and dihydrostreptomycin for two weeks. Eighteen of these patients remained well during follow-up periods of three to twenty-four months without treatment failures or relapses in the living patients; 1 patient had a reinfection with the same organism a year later and was cured with erythromycin, 2 gm. daily for two weeks. There were 5 deaths, all due to cardiac complications. The authors concluded that 1,000,000 units of aqueous procaine penicillin G and 1 gm. of dihydrostreptomycin sulfate given intramuscularly every twelve hours for two weeks represented adequate and curative treatment for subacute bacterial endocarditis caused by penicillin-sensitive streptococci. The strains of streptococci were sensitive to 0.1 unit per cubic centimeter or less, except in 1 case in which the organism required 0.2 unit.

At the recent Antibiotic Symposium, Jones and Yow[347] described the use of erythromycin alone or in combination with other antibiotics in 9 consecutive cases of bacterial endocarditis that had failed to respond to usual therapeutic regimens. Erythromycin had a suppressive effect in 1 patient with subacute staphylococcal endocarditis, but had no effect in 1 patient with enterococcal endocarditis and in another with acute staphylococcal endocarditis. In combination with streptomycin, erythromycin produced a prompt clinical and bacteriologic response in 3 patients with streptococcal endocarditis and in 1 patient with staphylococcal endocarditis; this combination was ineffective in only 1 case, in which the etiologic agent could not be isolated. Erythromycin combined with bacitracin was effective in 1 patient with streptococcal (microaerophilic) endocarditis.

References

175. Blake, F. G., Friou, G. J., and Wagner, R. R. Clinical observations on terramycin. *Yale J. Biol. & Med.* **22**:495-507, 1950.
176. Sayer, R. J., Michel, J. C., Moll, F. C., and Kirby, W. M. M. Terramycin: clinical, pharmacologic and bacteriologic studies. *Am. J. M. Sc.* **221**:256-263, 1951.
177. Arnold, W. P., Jr., and Reeves, R. L. Terramycin in treatment of subacute bacterial endocarditis: case report. *Antibiotics & Chemother.* **1**:181-184, 1951.
178. Rantz, L. A. Bacteroides endocarditis: report of case successfully treated with terramycin. *J. A. M. A.* **147**:124, 1951.
179. Editorial. New generic names for antibiotics. *New Eng. J. Med.* **249**:503, 1953.
180. Gocke, T. M., and Finland, M. Cross-resistance to antibiotics: effect of repeated exposure of bacteria to aureomycin, terramycin, chloramphenicol or neomycin on resistance to all of these antibiotics and to streptomycin and penicillin. *J. Lab. & Clin. Med.* **38**:719-735, 1951.

181. Curtin, M. Chloramphenicol in subacute bacterial endocarditis. *Lancet* 2:804, 1950.

182. Spring, M., and Wardell, H. Tetralogy of Fallot with subacute bacterial endocarditis: successful treatment with Chloromycetin. *Am. Heart J.* 43:918-921, 1952.

183. Garrido Lecca, G., and Tola, A. Subacute bacterial endocarditis treated with chloramphenicol and oxytetracycline. *J. A. M. A.* 152:913, 1953.

184. Heilman, F. R., Herrell, W. E., Wellman, W. E., and Geraci, J. E. Some laboratory and clinical observations on new antibiotic, erythromycin (Ilotycin). *Proc. Staff Meet., Mayo Clin.* 27:285-304, 1952.

185. Haight, T. H., and Finland, M. Laboratory and clinical studies on erythromycin. *New Eng. J. Med.* 247:227-232, 1952.

186. *Idem.* Resistance of bacteria to erythromycin. *Proc. Soc. Exper. Biol. & Med.* 81:183-188, 1952.

187. Smith, J. W., Dyke, R. W., and Griffith, R. S. Absorption following oral administration of erythromycin. *J. A. M. A.* 151:805-810, 1953.

188. Herrell, W. E., Nichols, D. R., and Martin, W. J. Erythromycin for infections due to *Micrococcus pyogenes*. *J. A. M. A.* 152: 1601-1606, 1953.

189. Hewitt, W. L., and Wood, J. P., Jr. Laboratory and clinical experience with carbomycin. *New Eng. J. Med.* 249:261-269, 1953.

190. Purcell, E. M., Wright, S. S., and Finland, M. Antibiotic combinations and resistance to antibiotics: penicillin-erythromycin and streptomycin-erythromycin combinations *in vitro*. *Proc. Soc. Exper. Biol. & Med.* 82:124-131, 1953.

191. Friedberg, C. K. Subacute bacterial endocarditis: revision of diagnostic criteria and therapy. *J. A. M. A.* 144:526-533, 1950.

192. Hildebrand, E., and Priest, W. S. Cardiac lesions in subacute bacterial endocarditis treated with penicillin: report of nine cases. *Am. J. Clin. Path.* 17:345-364, 1947.

193. Jones, M. Subacute bacterial endocarditis of nonstreptococcic etiology: review of literature of thirteen year period 1936-1948, inclusive. *Am. Heart J.* 40:106-116, 1950.

194. Oppenheimer, B. S., and Lubby, A. L. Arrest by penicillin of two cases of subacute bacterial endocarditis, due respectively to anaerobic staphylococcus, and to Streptococcus viridans. *J. Mt. Sinai Hosp.* 12:541-554, 1945.

195. Dowling, H. F., and Murray, F. J. Incidence and cost of treatment of bacterial endocarditis: study of all cases occurring in metropolitan Washington in year 1948. *Am. J. M. Sc.* 221:612-617, 1951.

196. Parsons, W. B., Jr., Cooper, T., and Scheifley, C. H. Anemia in bacterial endocarditis. *J. A. M. A.* 153:14-16, 1953.

197. Mallén, M. S., Hube, E. L., and Brenes, M. Comparative study of blood cultures made from artery, vein, and bone marrow in patients with subacute bacterial endocarditis. *Am. Heart J.* 33: 692-695, 1947.

198. Geraci, J. E. Antibiotic therapy of bacterial endocarditis. II. Current trends in treatment of subacute bacterial endocarditis. *Minnesota Med.* 35:861-866, 1952.

199. Geraci, J. E., and Manning, P. R. Antibiotic therapy in bacterial endocarditis. III. Penicillin O and hypoallergenic penicillins in treatment of subacute bacterial endocarditis. *Minnesota Med.* 36:466-470, 1953.

200. Gulotta, G. A., and Pascucci, S. E. Subacute bacterial endocarditis in rheumatic colony. *Bull. St. Francis San.* 9:43-48, 1952.

201. Numainville, L. J., and Scarpellino, C. J. Coexistent rheumatic fever and subacute bacterial endocarditis treated with ACTH and antibiotics. *Am. Heart J.* 43:468-473, 1952.

202. Ravina, A., Pestel, M., Poncelet, P., and Laplanche, C. Influence défavorable de l'ACTH, puis de la cortisone sur l'évolution d'une endocardite infectieuse à hémoculture négative. *Bull. et mém. Soc. méd. hôp. de Paris* 68:814-818, 1952.

203. Siguier, F., Welti, J-J., Blanguernon and Chimènes. Maladie d'Osler post-cortisonique. *Bull. et mém. Soc. méd. hôp. de Paris* 68:983-987, 1952.

204. Suzman, M. M. Clinical application of corticotropin and cortisone therapy: review of 247 cases. *S. African M. J.* 27:195-212, 1953.

205. Kass, E. H., and Finland, M. Adrenocortical hormones in infection and immunity. *Ann. Rev. Microbiol.* 7:361-388, 1953.

206. Gilchrist, A. R., and Mercer, W. Infective endarteritis of pulmonary artery. *Lancet* 2:267-272, 1947.

207. Lichtman, P., and Master, A. M. Incidence of valvular heart disease in people over fifty and penicillin prophylaxis of bacterial endocarditis. *New York State J. Med.* 49:1693-1698, 1949.

208. Rhoads, P. S. Subacute bacterial endocarditis: etiologic considerations and prophylaxis. *M. Clin. North America* 32:176-186, 1948.

209. Mendelson, C. L. Pregnancy and subacute bacterial endocarditis. *Am. J. Obst. & Gynec.* 56:645-654, 1948.

210. Pedowitz, P., and Hellman, L. M. Pregnancy and healed subacute bacterial endocarditis. *Am. J. Obst. & Gynec.* 66:294-301, 1953.

211. Roth, O., et al. Chlortetracycline (Aureomycin) in prevention of bacteremia following surgery: attempt to prevent subacute bacterial endocarditis in patients with heart disease. *Arch. Int. Med.* 92:485-489, 1953.

212. Palmer, H. D., and Kempf, M. Streptococcus viridans bacteremia following extraction of teeth: case of multiple mycotic aneurysms in pulmonary arteries: report of cases and necropsies. *J. A. M. A.* 113:1788-1792, 1939.

213. Ernstene, A. C., McGarvey, C. J., and Ecker, J. A. Prophylaxis of subacute bacterial endocarditis. *Cleveland Clin. Quart.* 18:1-5, 1951.

214. Northrop, P. M., and Crowley, M. C. Further studies on effect of prophylactic use of sulfathiazole and sulfamerazine on bacteremia following extraction of teeth. *J. Oral Surg.* 2:134-140, 1944.

215. Bender, I. B., and Pressman, R. S. Factors in dental bacteremia. *J. Am. Dent. A.* 32:836-853, 1945.

216. Rhoads, P. S., Schram, W. R., and Adair, D. Bacteremia following tooth extraction: prevention with penicillin and NU 445. *J. Am. Dent. A.* 41:55-61, 1950.

217. Glaser, R. J., Dankner, A., Mathes, S. B., and Harford, C. G. Effect of penicillin on bacteremia following dental extraction. *Am. J. Med.* 4:55-65, 1948.

218. Northrop, P. M. Penicillin therapy in oral surgery. *J. Oral Surg.* 7: 39-55, 1949.

219. Hirsh, H. L., Vivino, J. J., Merril, A., and Dowling, H. F. Effect of prophylactically administered penicillin on incidence of bacteremia following extraction of teeth: results in patients with healed rheumatic and bacterial endocarditis. *Arch. Int. Med.* 81: 868-878, 1948.

220. Solowey, M. Serological classification of viridans streptococci with special reference to those isolated from subacute bacterial endocarditis. *J. Exper. Med.* 76:109-126, 1942.

221. Levin, M. D. Dental surgery as prophylactic in subacute bacterial endocarditis: preliminary report of seven consecutive successfully treated cases. *J. Am. Dent. A.* 32:307-318, 1945.

222. Hunter, T. H. Treatment of subacute bacterial endocarditis. *Modern Concepts of Cardiovas. Dis.* 15: No. 8, 1946.

223. Lipman, M. O., Coss, J. A., Jr., and Boots, R. H. Changes in bacterial flora of throat and intestinal tract during prolonged oral administration of penicillin. *Am. J. Med.* 4:702-709, 1948.

224. Krumwiede, E. Penicillin resistance of nonhemolytic streptococci from rheumatic children receiving prophylactic penicillin. *Pediatrics* 4:634-642, 1949.

225. Meads, M., Rowe, W. P., and Haslam, N. M. Alterations in bacterial flora of throat during oral therapy with aureomycin. *Arch. Int. Med.* 87:533-540, 1951.

226. Jackson, G. G., et al. Terramycin therapy of pneumonia: clinical and bacteriologic studies in 91 cases. *Ann. Int. Med.* 35:1175-1202, 1951.

227. Womack, N. R., et al. Terramycin therapy of urinary tract infections. *Arch. Int. Med.* 89:240-257, 1952.

228. Touroff, A. S. W. Rationale of operative treatment of subacute bacterial endarteritis superimposed on patent ductus arteriosus. *Am. Heart J.* 23:847-856, 1942.

229. Vesell, H., and Kross, I. Patent ductus arteriosus with subacute bacterial endarteritis: diagnosis and indications for operation. *Arch. Int. Med.* 77:659-677, 1946.

230. Gross, R. E. Patent ductus arteriosus: observations on diagnosis and therapy in 525 surgically treated cases. *Am. J. Med.* 12: 472-482, 1952.

231. Starer, F. Analysis of 50 cases of persistent ductus arteriosus. *Brit. M. J.* 1:971-973, 1953.

232. Kinsella, R. A. Chemotherapy of bacterial endocarditis. *Ann. Int. Med.* 15:982-986, 1941.

233. Jones, S. H., and Tichy, F. Bacterial endocarditis treated with penicillin: observations in nine cases. *New Eng. J. Med.* 236: 729-736, 1947.

234. Rosenberg, C. A. Rupture of splenic infarct and sudden death complicating course of subacute bacterial endocarditis. *Am. J. Med.* 5:143-147, 1948.

235. Fellinger, K. Milzexstirpation zur Unterstützung der Penicillintherapie bei bakterieller Endokarditis. *Wien. klin. Wchnschr.* 60:509, 1948.

236. Lipton, S., and Miller, H. Streptococcus viridans septicemia — subacute bacterial endarteritis of arteriovenous aneurysm. *J. A. M. A.* 126:766-769, 1944.

237. McMillan, R. L. Subacute bacterial (Streptococcus viridans) endocarditis treated with penicillin. *Am. J. Med.* 1:628-633, 1946.

238. Hurwitz, A., and Arst, D. B. Mycotic aneurysm of brachial artery after cure of bacterial endocarditis: successful treatment by surgical excision. *New Eng. J. Med.* 238:903-905, 1948.

239. Scott, H. W., Jr., and Williams, J. M., Jr. Multiple arterial emboli: three successful embolectomies in case of bacterial endocarditis. *Arch. Surg.* 58:28-34, 1949.

240. Heckler, G. B., and Tikellis, I. J. Acquired arteriovenous fistula with subacute bacterial endocarditis and endarteritis. *J. A. M. A.* 150:1301-1304, 1952.

241. Kahn, J. W., Livingston, S. F., and Charet, R. Arteriovenous fistula and septicemia cured by excision and antibiotics. *Am. J. Surg.* 86: 175-180, 1953.

242. Davis, M. E., and Wortmann, R. F. Subacute bacterial endocarditis during pregnancy. *Am. J. Obst. & Gynec.* 53:878-880, 1947.

243. Slater, J. L. Recurrence of subacute bacterial endocarditis complicated by pregnancy. *Permanente Found. M. Bull.* 9:149-152, 1951.

244. Leaman, W. G., Wikingsson, M. B., Webster, M. B., and Shaw, C. C. Caronamide and penicillin in subacute bacterial endocarditis due to *Streptococcus faecalis*. *Ann. Int. Med.* 30:646-654, 1949.

245. deHay, R. M., Bell, J. L., and Beebe, J. M. Bacteroides bacterial endocarditis: cure by massive doses of penicillin. *Hawaii M. J.* 9: 235-237, 1950.

246. Geraci, J. E., and Martin, W. J. Antibiotic therapy of bacterial endocarditis. IV. Successful short-term (two weeks) combined penicillin-dihydrostreptomycin therapy in subacute bacterial endocarditis caused by penicillin-sensitive streptococci. *Circulation* 8: 494-509, 1953.

247. Jones, L. C., and Yow, E. M. Effect of erythromycin alone and in combination with streptomycin in endocarditis. In *Antibiotics Annual, 1953-1954*. Edited by H. Welch and F. Marti-Ibanez. 632 pp. New York: Medical Encyclopedia, Incorporated, 1953. Pp. 464-469.

MEDICAL INTELLIGENCE

BRACHIAL PALSY AFTER MANIPULATION OF FROZEN SHOULDER*

HENRY MILCH, M.D.†

NEW YORK CITY

THE clinical entity of "frozen shoulder" is well known, but there is no unanimity of opinion about its etiology, pathogenesis, pathology or even treatment. Although most students have classed it with the more generic group of periarthridites described by DuPlay, DePalma[1] has expressed the opinion that it is essentially a bicipital tendonitis, and Neviaser,[2] specifically denying the periarthritic classification, has designated it an "adhesive capsulitis." Corresponding to these varied concepts of the condition, therapy has been most diverse. Among the more radical measures surgical release of the capsule and detachment of the biceps tendon at the supraglenoid tubercle and its reattachment to the coracoid process, with division of the coracoacromial ligament, have been advised. Among the more conservative measures cortisone, local anesthesia, heat, x-ray therapy, rest and manipulation have been suggested.

Although each case must be considered individually, it is generally conceded that in the refractory cases gentle manipulation under anesthesia is of value and may preclude the possibility of more radical surgical intervention. Harmon et al.[3] described 292 patients with painful frozen shoulder who were treated by conservative physical methods, including exercises or gentle manipulation under anesthesia. In 105 cases the patients seemed to benefit more from active exercise after manipulation. Neviaser[2] reported that during manipulation of the shoulder under anesthesia in the course of open operations the capsule could be separated from the head in much the same way that adhesive plaster could be torn away from the skin; once the separation had occurred, motion of the head within the joint was free. On the other hand, DePalma[1] has expressed the contrary opinion that manipulation of frozen shoulders was dangerous and futile. All his patients whose shoulders were manipulated under direct vision, however gently, showed tears of varying degree.

*From the Second Orthopedic Service, Hospital for Joint Diseases.

†Attending orthopedic surgeon-in-charge, Second Orthopedic Service, Hospital for Joint Diseases.

Although these opposite opinions may be most distressing to the patient and may, indeed, serve as the basis for unjustified legal action against competent and conscientious physicians, they stress the necessity for wider recognition of the sequelae of even so generally employed a procedure as manipulation of the frozen shoulder. All who have had experience with this form of therapy are well aware of its dangers, especially that of fracture. Because of bone atrophy associated with pain-induced disuse, fracture of the surgical neck or shaft, such as that noted during the Kocher method of reducing shoulder dislocations, is an ever-present threat. Another, fortunately rare, complication — traction paralysis of the brachial plexus[4] — occurred in the following cases.

CASE REPORTS

CASE 1. I. H., a 52-year-old man, was admitted to the hospital in May, 1951, complaining of pain and limitation of motion in the right shoulder of 3 months' duration. Examination disclosed limitation of abduction at 90°, with some limitation of both internal and external rotation. There were no signs of cervical-nerve dysfunction. Reflex reactions and sensory perception were physiologic. A roentgenogram of the shoulder failed to disclose calcification.

Several days after admission, the right upper extremity was gently manipulated under general anesthesia through a full range of motion at the shoulder. During the course of the manipulation several loud snapping sounds were heard. The patient was returned to bed, and the arm was held tied to the head of the bed. On the following day he seemed to have power in the deltoid muscle, but 1 week later, when the arm was adducted, it was observed that power in the right deltoid muscle was completely absent. There was definite weakness in the elbow and in the fingers, with slight sensory hypesthesia in the distribution of the 5th cervical root to the shoulder and thumb.

Electric testing revealed partial paralysis of the muscles of the arm and forearm. A neurosurgical consultant expressed the opinion that an incomplete traction injury to the brachial plexus had occurred.

The arm was supported in an abduction splint, and electric therapy was instituted. In June, 1951, barely 3 weeks after the initial injury, there was evidence of some improvement. One week later active abduction of the shoulder was possible to 125°. By July 3 normal power and sensation had been restored to the fingers, and 2 days later, the patient was discharged to the Out-Patient Department for ambulant therapy. Progress was continuous, and in October, treatment was discontinued after complete restoration of normal motion.

CASE 2. A 38-year-old physician was admitted to the hospital in October, 1951. During the preceding July a young patient had jumped on his neck and shoulders. In attempting to protect himself the patient had violently contracted his shoulder muscles. He complained of a feeling of dullness on the right side of the neck posteriorly, pain in the right ear when the mouth was opened widely and limitation of motion in the right shoulder owing to pain. He was given local therapy by a colleague but without relief.

On admission to the hospital, all motions of the cervical spine were normal. Neither arm could be raised directly overhead or extended laterally to beyond the horizontal level. Palpation elicited tenderness over the musculotendinous cuff on the right side, with no evidence of motor, sensory or reflex impairment in the rest of the extremity. The left shoulder presented no tenderness. Roentgenograms, however, revealed calcification in the region of the supraspinatous tendons bilaterally.

The patient was placed in balanced traction. On October 29 another colleague gently manipulated both shoulders under general anesthesia, with audible snapping of several adhesions. After this procedure the patient complained of severe pain. On November 3 the right arm could not be raised or supported when passively raised. There was tenderness over the right deltoid tubercle, with no evidence of any sensory impairment. There

was numbness in the 4th and 5th fingers of the left hand, pain along the volar and ulnar aspects of the left forearm and tenderness in the intercondylar fossa.

The patient was given an abduction splint to the right shoulder and was discharged from the hospital on November 7. He was subsequently given electrotherapy and exercises. During the early part of 1952, he gave the information that sensation was beginning to return in the previously hypesthetic areas of the left hand, with return of some power in the right deltoid. Examination confirmed these statements although it was evident that a weakness of the right deltoid muscle persisted.

Because of the evidence of early return of sensory perception and beginning improvement in the power of the deltoid muscle the prognosis was considered favorable. It was not possible to re-examine the patient to determine whether a complete functional restitution was obtained.

Discussion

Traction paralysis in the distribution of the whole brachial plexus or any of its component parts is not uncommon after injury about the shoulder. It is the recognized cause of birth palsies and has been reported to occur in about 15 per cent of even simple dislocations of the humerus.[4]

The extent of involvement of the forearm and fingers in both the cases reported above must be predicated upon traction on the entire plexus. The greater incidence of axillary-nerve involvement must be explained as resulting from the short course of this nerve as it winds around the capsule of the shoulder joint.

Indeed, a recent resident at the hospital invariably manifested axillary-nerve paralysis simply by holding his hands on his head with the arms in external rotation for a short time.

Although prognosis is usually good, it should be guarded. The ultimate outcome, of course, depends on whether simple traction or complete avulsion of the root and trunk has occurred. Early signs of improvement in sensory perception or motor power should be regarded as evidence of only partial injury owing to traction. In such cases mechanical support to prevent stretching of muscles and electric stimulation may be expected to result in satisfactory restoration of function.

Summary and Conclusions

Two cases of brachial-plexus injury after manipulation of frozen shoulder are presented. Although unusual this is a completely explicable sequel and complication of manipulation about the shoulder. The paralysis that results is usually transitory and does not seem to afford a satisfactory reason for abandoning a method that experience has validated in the treatment of many painful frozen shoulders.

References

1. DePalma, A. F. Loss of scapulohumeral motion (frozen shoulder). *Ann. Surg.* 135:193-204, 1952.
2. Neviaser, J. S. Adhesive capsulitis of shoulder: study of pathological findings in periarthritis of shoulder. *J. Bone & Joint Surg.* 27:211-222, 1945.
3. Harmon, P. H., Merryman, G. H., and Neuru, E. N. Results from treatment of 540 painful shoulders: follow-up study of recoveries with special attention to tendon calcification, frozen shoulders and measures for relief of pain. *Permanente Found. M. Bull.* 8:60-71, 1950.
4. Milch, H. Primary brachial palsy following dislocation of shoulder. *Am. J. Surg.* 5:66-72, 1928.

Massachusetts Physicians Art Society

24. Roman Ruins

Exhibited at American Medical Association, Atlantic City, 1951

Award of Merit
Opaque White on Black by

Conrad Nobili, M.D.

Associate in Allergy, Boston Dispensary;
Secretary, Massachusetts Physicians Art Society

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40101

PRESENTATION OF CASE

A twenty-seven-year-old fireman was admitted to the hospital because of pain in the right thigh.

The patient was well until a month before admission, when pain occurred suddenly while he was carrying a stretcher to an ambulance. The pain recurred when he walked or carried things, and was relieved by rest. Since the onset of pain, there had been a slight limp. Heat and diathermy did not relieve or aggravate the condition. The character and intensity of the pain had not changed recently; he had no night pain.

The past history was noncontributory except for a splenectomy at nine years of age because of a ruptured spleen, apparently traumatic in origin.

On physical examination the patient walked with a slight limp to the left. There was 0.6-cm. atrophy of the right thigh at the level of the gluteal crease, and 1.3-cm. atrophy in the midthigh. The calves were of equal size. The right buttock was markedly wasted. There was no limitation of movement in the right hip or knee, and no mass or tenderness could be found in the right thigh. The Trendelenburg sign was negative bilaterally.

The temperature, pulse and respirations were normal. The blood pressure was 155 systolic, 85 diastolic.

The urine had a specific gravity of 1.018 and was negative for albumin. Bence-Jones protein was not present. Examination of the blood showed a hemoglobin of 16.8 gm. per 100 cc. and a white-cell count of 8600, with 67 per cent neutrophils, 29 per cent lymphocytes and 4 per cent monocytes. The platelets were slightly increased in number. The sedimentation rate was 3 mm. in sixty minutes. The serum calcium was 9.5 mg., the phosphorus 4.6 mg., the alkaline phosphatase 2.1 units, the total protein 5.6 gm., the albumin 3.6 gm., and the globulin 2.0 gm. per 100 cc. An old-tuberculin skin test in a dilution of 1:10,000 was positive.

A roentgenogram of the chest was normal. Multiple views of the right femur revealed an osteolytic lesion of the shaft measuring 10 cm. in length and extending from a level just above the lesser trochanter distally (Fig. 1). There was thinning of the cortex from within and apparently trabecular calcification within the radiolucent area although this could have represented residual cortical bone that had been completely eroded. The margins were not sharply defined, and there appeared to be some early periostitis along the anterior portion of the shaft and possibly medially below the lesser trochanter.

FIGURE 1. *Roentgenogram of the Femur, Showing a Large Lytic Lesion of the Proximal Shaft Extending into the Intratrochanteric Area.*

The arrow points to thinned cortex.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOHN E. GARY*: I should like to begin the discussion by considering the x-ray films. The lesion that caused the symptoms is a large mass that has replaced the normal medullary contents of the upper right femoral shaft (Fig. 1). It is circumscribed both below and above, although faintly, and has thinned but neither expanded nor destroyed the cortex. The cortex appears intact except that anteriorly

*Associate radiologist, Mount Auburn Hospital, Cambridge.

it is slightly roughened and some new bone has formed on its external surface. The femur above and below is normal in appearance. I think this irregularity in the cortex was due to an incomplete fracture that occurred when the patient lifted the stretcher a month before admission. If he had an incomplete fracture with hemorrhage into the mass, that would account both for the sudden onset of the pain and for its relief by rest. The second set of films, taken a week later, shows erosion of the cortex laterally — the cortex, which was intact, now appears to have a hole in it. I think the erosion of the bone occurred over an area of hemorrhage into the mass. The third set of films, taken another week later, demonstrates a definite pathologic fracture. I believe the wasting of the buttock and thigh was atrophy from disuse, particularly in view of the normal Trendelenburg test.

A number of diagnoses come to mind, some of which I can rule out by use of the information given. Tuberculosis occurring in the shaft of the bone without joint involvement is rare indeed. This and the normal chest film, normal sedimentation rate and lack of anemia and night pain are the reasons for excluding tuberculosis. Cryptococcosis, the only other bone infection that I know of that causes a purely osteolytic lesion, I shall rule out on the same basis as tuberculosis.

Hyperparathyroidism is effectively eliminated, I believe, by the normal serum calcium, phosphorus and phosphatase as well as by the films that show a normal femur above and below the lesion.

From now on it becomes more difficult to rule out possible diagnoses, and some cannot be excluded with certainty. Against a malignant bone tumor is the normal sedimentation rate and lack of anemia. Some malignant bone tumors, however, can produce the x-ray changes that were present. Only those that arise in the medulla of the bone need be considered. A plasma-cell myeloma I shall rule out because of the normal laboratory studies: the serum protein was low, and there was no Bence-Jones protein in the urine. Moreover, myeloma usually occurs in an older age group.

Ewing's sarcoma is a tumor of younger persons. It would be highly unusual to see it localized at one end of the medullary canal or eroding the cortex of bone without extensive periosteal new-bone formation. Reticulum-cell sarcoma usually causes irregular destruction and is not so well circumscribed as the tumor was in this case. Osteogenic sarcoma can arise in the medulla and would adequately account for the grossly trabeculated bone. However, it usually produces widespread and irregular destruction of the cortex, which usually has a ragged inner surface. Here the cortex was rather smooth. A chondrosarcoma, particularly one that arose in a previously existing enchondroma, could result in the x-ray changes. These tumors vary a great deal in their rate of growth. Some grow very slowly and therefore may not be associated with constitutional symptoms, as in this case. Of all the malignant tumors chondrosarcoma would be my first choice. Against a primary sarcoma of the bone is the lack of a palpable mass and of tenderness over the lesion.

Metastatic carcinoma I shall exclude because of the patient's youth, the lack of constitutional symptoms, the normal laboratory findings and the normal sedimentation rate.

Of the malignant lymphomas, lymphosarcoma most often produces destructive lesions in bone, but again there are usually mutliple lesions and there is more widespread destruction of the cortex.

Among the benign conditions is giant-cell tumor, which is rarely seen except in the epiphysis. When it occurs in the shaft, it is usually eccentric and expands the bone eccentrically. A nonosteogenic fibroma of the bone is almost always eccentric, and its margins are usually sharply etched by reactive bone.

I come, then, to four conditions from which I do not think I can choose with any certainty. The first, eosinophilic granuloma, is usually a smaller lesion than the one seen in this case. The lesions frequently are multiple, and the patients may have leukocytosis and eosinophilia, which were not present here. I shall not select eosinophilic granuloma. The second is an enchondroma. The patient was in the correct age group. These lesions are frequently present in the femoral shaft, but they usually begin nearer to the epiphysis, involve the femoral neck and also expand the bone. Because these findings were not present I shall not choose enchondroma. A simple bone cyst often occurs in the femoral shaft; that is one of its favorite locations. Cysts usually produce symptoms, however, before the age of twenty, quite frequently as the result of a pathologic fracture. Like the enchondroma, they usually begin near the epiphyseal line. I think that this would be a good choice, but I shall pick the final lesion of these four — namely, fibrous dysplasia. Some areas of this mass had the ground-glass appearance that is supposed to be typical of fibrous dysplasia; that appearance is caused by deposition of calcium in the fibrous tissue. Islets of bone may be present in the fibrous dysplasia, growing around trabeculae but leaving some intact. I am somewhat disturbed by the lack of expansion of the bone and by the fact that the margins were not sharply circumscribed.

In summary I believe that the patient had long had an osteolytic lesion in the upper end of the femur and that because of an unusual strain an already weakened cortex broke. I shall rule out infection and hyperparathyroidism. I think that a malignant tumor is unlikely because of the lack of constitutional symptoms and normal laboratory findings, and I shall pick fibrous dysplasia by a slim margin.

DR. WALTER BAUER: Do you think there is any possibility of a hemangioma?

DR. GARY: I do not know if I can rule out that lesion from the films. I think hemangiomas occur more frequently in vertebras.

DR. BAUER: I just went over a series of them with Gorham,[1] who collected many of the cases reported in the literature and obtained histologic sections from the authors. The collection was quite impressive.

DR. BENJAMIN CASTLEMAN: We have had 2 cases, 1 in a fibula and 1 in another long bone, in both of which there was quite a large expansion of cortex such as is seen in a giant-cell tumor.

DR. BAUER: Many in Gorham's series did not show expansion of the cortex. I was wondering whether the islands of bone formation seen in these films would be against a hemangioma.

DR. GARY: I cannot say for certain that that is new-bone formation within the lesion. It could just as well be located along the posterior cortex external to the mass. As one looks at the coarsely trabeculated bone, he is looking at a third of the circumference of a circle; therefore, the bone could be remaining cortex all the way around and not new-bone formation. The trabeculae are quite coarse, however, and could be new bone.

DR. BERNARD M. JACOBSON: Although the age of the patient is against myeloma, the so-called solitary benign plasmoma does occur in the absence of Bence-Jones protein and hyperproteinemia. Several years ago Dr. Otto E. Aufranc removed one from the midshaft of the tibia in a man of twenty-four. In that case all the other findings were negative.

DR. GARY: Has that patient had another tumor since?

DR. JACOBSON: No; but the tumor was treated radically by complete resection and bone graft. The patient was seen about a year and a half later and had no other myeloma.

DR. GARY: I have always been rather sceptical about a solitary plasmoma or myeloma. Have you seen them, Dr. Castleman?

DR. CASTLEMAN: I remember the case referred to by Dr. Jacobson. That patient was still well over five years after the operation.

DR. BAUER: What did Dr. Laurence L. Robbins say about this case?

DR. CASTLEMAN: Dr. Robbins and I both saw this patient in the tumor clinic. I thought this was a bone cyst before operation; Dr. Robbins's first diagnosis was a chondrosarcoma.

CLINICAL DIAGNOSIS

?Chondrosarcoma.
?Bone cyst.

DR. JOHN E. GARY'S DIAGNOSIS

Fibrous dysplasia.

ANATOMICAL DIAGNOSIS

Plasma-cell myeloma, solitary.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At operation pink, fleshy material was scooped out, and this proved to be a plasma-cell myeloma. This section shows the diffuse cellularity and very mature plasma cells (Fig. 2). Christopherson and Miller[2] collected 25 cases from the literature, including 3 of their own, of so-called solitary myeloma, which admittedly is a dangerous diagnosis to make; these patients were followed for more than three years after excision, curettage or x-ray treatment without any evidence of recurrence or other lesions. Any sort of treatment in this group

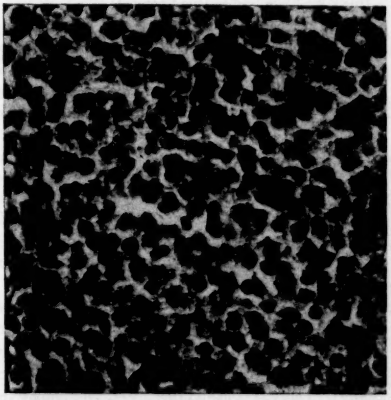

FIGURE 2.

seemed to have the same end result, and there have been cases continuing as long as fifteen years after treatment. It would be helpful if we, as pathologists, could predict from the histology whether a myeloma is solitary or one of the much more common forms in which it appears in other bones later on. The study of Christopherson and Miller[2] showed that the cases in which the cells are quite undifferentiated plasma cells rather than mature plasma cells are the ones that always end up as cases of multiple myeloma. The well differentiated form may also end up as a multiple myeloma, but all the so-called solitary lesions that have been reported have been composed of mature plasma cells. The fact that the patient under discussion was a young person and the histology was the mature form of plasma cell may augur well for him.

DR. BAUER: What was done?

DR. CASTLEMAN: A curettage, followed by insertion of bone chips; I do not know whether x-ray treatment was to be given or not.

DR. LAURENCE L. ROBBINS: X-ray treatment has already been given.

DR. BAUER: Are the other forms of therapy not adequate?

DR. CASTLEMAN: From the review by Christopherson and Miller,[2] if a lesion is of the solitary type, x-ray therapy might not be indicated since many cures were reported with curettage alone. We believe that myeloma does not metastasize but appears independently in various bones. I should therefore not advise anything radical such as an amputation.

DR. JACOBSON: How many authentic cases of localized myeloma at the time of operation do you think we have had in this hospital?

DR. CASTLEMAN: We have had at least 3; in 2 the myelomas were excised twenty and thirty years ago; they were reported then in the Bone Tumor Registry collection. We have heard nothing more from the patients and are now checking on their follow-up study.

DR. ROBBINS: Another patient had a myeloma in the clavicle that was excised, and it was called solitary; it was not until four years later that other bone lesions that were recognizable in the x-ray films developed. Approximately ten years after the excision of the clavicle she died with a full-blown multiple myeloma.

DR. CASTLEMAN: The microscopical appearance of the myeloma in that case[3] was the undifferentiated form — not the form with mature plasma cells.

DR. ROBBINS: Are there really any solitary myelomas? There is considerable scepticism among those who have studied bone tumors that there is such an entity.

DR. CASTLEMAN: Of the 25 patients who had apparently solitary lesions after a three-year follow-up period[2] there was no evidence of further disease after five years in 15 and after ten years in 5. I think that is good evidence that the original lesion was solitary.

DR. BAUER: Some patients with multiple myeloma live a long time.

DR. CASTLEMAN: That is true, but there is usually disseminated disease.

REFERENCES

1. Gorham, L. W. Unpublished data.
2. Christopherson, W. M., and Miller, J. A. Re-evaluation of solitary plasma-cell myeloma of bone. *Cancer* 3:240-252, 1950.
3. Case Records of the Massachusetts General Hospital (Case 39352). *New Eng. J. Med.* 249:376-380, 1953.

CASE 40102

PRESENTATION OF CASE

First admission. A fifty-year-old Italian shoe worker was admitted to the hospital because of massive hematemesis.

A month before admission he had noted the sudden onset of melena, and the next night he had been awakened by the urge to defecate. He got up and vomited large amounts of bright-red blood and clots four times.

For ten years he had had epistaxes once or twice a month. For many years he had drunk wine or beer in moderate amounts almost every day and about 10 ounces of whisky a week.

Physical examination showed a pale but well developed and well nourished man. The heart and lungs were normal. The liver border was palpable one fingerbreadth below the right costal margin, and the spleen two fingerbreadths below the left costal margin. There was slight ankle edema.

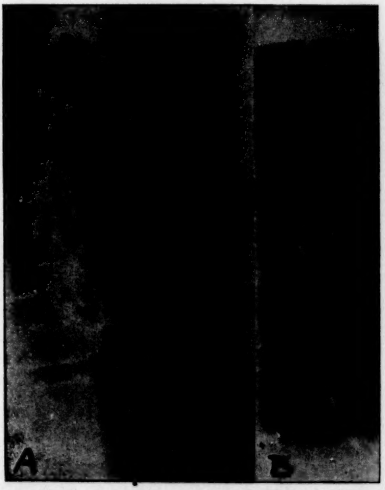

FIGURE 1. *Roentgenograms of the Esophagus, Showing Varices* (A), *Which Are Smaller after the Splenorenal Shunt* (B).

The temperature was 98°F., the pulse 85, and the respirations 27. The blood pressure was 140 systolic, 65 diastolic.

Urinalysis was negative. Examination of the blood disclosed a red-cell count of 3,200,000, with a hemoglobin of 14 gm. per 100 cc., and a white-cell count of 4100, with 80 per cent neutrophils. The stools were repeatedly guaiac negative. A barium-swallow examination demonstrated multiple beaded, linear, soft, elevated areas characteristic of varices in the lower two thirds of the esophagus (Fig. 1*A*).

The stomach and duodenum were negative. A roentgenogram of the chest was normal. The patient was discharged on the third day.

Second, third and fourth admissions (three, nine and ten years later). The second admission, lasting thirteen days, was for a poorly explained episode of epigastric pain. Abnormal laboratory findings at that time included a prothrombin time of 29 seconds (normal, 20 seconds) and a cephalin flocculation of ++++ in forty-eight hours. The third admission was because of black stools. Diabetes had been discovered six months before and had been controlled by diet; however, on admission the urine gave a +++ test for sugar, and the fasting blood sugar was 198 mg. per 100 cc. Other laboratory studies were essentially as before. A barium-enema examination was negative; proctoscopy to a depth of 15 cm. revealed spasm and a mucosa that bled with moderate trauma. The patient improved on protamine zinc insulin, a high-calorie diet and other supportive measures. The fourth admission was for another episode of rectal bleeding. On physical examination he was pale, and the liver edge was palpated three fingerbreadths below the right costal margin. The blood hemoglobin was 8.5 gm. per 100 cc. Cephalin flocculation was negative; the prothrombin time was 19 seconds (normal, 16 seconds), and a stool guaiac test was +++. Otherwise, the findings were as before. He was given transfusions, after which he became asymptomatic. A needle biopsy of the liver was reported as showing "portal cirrhosis." He was discharged on the twenty-second day to return to the Gastrointestinal Clinic for consideration of a portacaval shunt.

Fifth admission (two years later). He had been well and working until two weeks before admission, when his entire family had "gastroenteritis," with vomiting for three days. He was recovering from this illness when, on the morning of admission, he vomited a pint of dark, clotted blood.

Physical examination and laboratory data were unchanged, but he continued to vomit dark-red blood, and later that day the blood pressure dropped to 90 systolic, 60 diastolic. The hemoglobin was 8.5 gm. per 100 cc., with a hematocrit of 29 per cent. He was supported with blood transfusions and an emergency esophagotomy with suture of esophageal varices was performed. Except for a transitory thrombophlebitis of the right great saphenous vein on the fourth postoperative day, convalescence was uneventful, and he was discharged on the thirteenth hospital day.

Sixth admission (three months later). He had done well since discharge except for slight epigastric "burning" after meals. He was admitted to the hospital for portacaval anastomosis. Physical examination was unchanged. The urine was normal. The hemoglobin was 14 gm., and the white-cell count 5000. The serum total protein was 7.02 gm., the albumin 3.88 gm., the globulin 3.14 gm., the nonprotein nitrogen 23 mg., the alkaline phosphatase 4.1 units, the fasting blood sugar 176 mg., and the bilirubin 0.5 mg. direct and 1.1 mg. total per 100 cc. Cephalin flocculation was ++ in forty-eight hours, and the prothrombin time 21 seconds (normal, 19.5 seconds). A stool was guaiac negative. On the third day a splenectomy, splenorenal-vein anastomosis and biopsy of the liver were done. Portacaval anastomosis could not be accomplished because of adhesions. After the spleen had been removed, the splenic-vein pressure was equivalent to 35 cm. of saline solution. After splenorenal shunt had been completed, the pressure was equivalent to 24 cm., and the renal-vein pressure to 11 cm. The liver was hobnail in appearance.

Pathological examination revealed portal cirrhosis of the liver of postnecrotic type; the spleen weighed 650 gm., and the sinusoids were dilated.

On the ninth postoperative day thrombophlebitis developed in the right common femoral vein, and bilateral ligation was done. The postoperative course was otherwise good, and a barium-swallow examination on the fourteenth day showed a decrease in the size of the varices (Fig. 1*B*). The patient was discharged on the twentieth hospital day.

FIGURE 2. *Barium-Enema Examination. Arrows indicate the area of relative narrowing in the sigmoid.*

Seventh admission (two years later). Since discharge he had done fairly well but had been too weak to work. There had been a tendency to constipation, and a month before admission, after a large dose of Epsom salts, a severe pain developed in the lower abdomen, worse on the right. The pain was dull and aching and temporarily relieved by his

daily bowel movement. Four days before admission he noticed streaking of his stools with bright-red blood, and began having two bowel movements a day. On the day of admission sigmoidoscopic examination was performed in the Out Patient Department, with normal findings to a level of 20 cm., but blood clots were seen coming from above this point, and he was admitted to the hospital.

Physical and laboratory findings were unchanged from the previous admission except for slight tenderness in the left lower quadrant.

A barium-enema examination showed definite narrowing of the high sigmoid loops (Fig. 2), with loss of the normal mucosal pattern; the loops appeared fixed. No diverticula or tumor mass was seen.

On the third hospital day, after being prepared for gastrointestinal x-ray films, he suddenly passed 450 cc. of bright-red blood by rectum. In the next two hours he passed 1275 cc. more, and mild shock developed. Blood transfusions were begun, and an operation was performed.

Differential Diagnosis

Dr. Perry J. Culver*: In discussing this case I feel like the man who sees the tip of the tail of a dog and is supposed to guess how large the dog is. I am told that the patient had portal cirrhosis of postnecrotic type and esophageal varices. The natural history of portal cirrhosis is given in great detail. One could make a teaching exercise out of this by discussing the portal cirrhosis, but the purpose of these exercises is to establish a diagnosis on the basis of the information given. Therefore, the problem is to determine the nature of the lesion that caused the bleeding from the rectum.

Interestingly enough, this man bled from esophageal varices over a period of twelve years until an operation was performed on the varices to stop the bleeding. In recent years, our attention seems to have been focused on the high mortality associated with esophageal varices, — somewhere between 45 and 50 per cent during the first year of bleeding, — and I think all of us are inclined to lose sight of the fact that a certain number of patients with cirrhosis and bleeding esophageal varices survive for a good many years. Ratnoff and Patek† found that about 46 per cent died within the first six months; 30 per cent survived during the first year, and between the first and fifth years the percentage of survivors decreased slowly to about 20 per cent at five years after the first hematemesis.

Another interesting point is the presence of diabetes before the last admission. The relation between cirrhosis and diabetes has been speculated upon. Ratnoff and Patek† say that about 5 per cent of patients with cirrhosis also have diabetes. It is obvious that with cirrhosis there will be some disturbance of sugar metabolism. On several occasions it has been noticed that as the cirrhosis becomes worse, the diabetes seems to be easier to control and the insulin requirement decreases. I do not know how to explain that on a physiologic basis.

During the third, fourth and fifth admissions rectal bleeding was mentioned. I think by rectal bleeding, melena is meant; dark stools were described on one occasion and +++ guaiac tests on others, but bright-red blood in the stools was not described. I believe, therefore, that the so-called rectal bleeding before the splenorenal shunt was probably bleeding from the esophageal varices and was probably unlike the bleeding that occasioned the last admission. It seems fair to assume that the mention of black stools refers to bleeding above the ileocecal valve. On the other hand, it is not safe to assume that bright-red blood or currant-jelly clots represented bleeding below the ileocecal valve because if the bleeding from the esophageal varices is massive enough, dark-red blood or currant-jelly clots may appear in the stools.

The state of the large bowel in the period before the shunt was mentioned only once. Sigmoidoscopic examination to a level of 15 cm. revealed spasm and a mucosa that bled with moderate trauma. I am not sure how significant that is. If the trauma were no more severe than wiping the bowel wall, there must have been a pathologic process in the rectal wall. This could be consistent with ulcerative colitis, one of the hallmarks of which (either idiopathic or specific) is friability of the wall of the bowel, with bleeding on wiping. This may have been an artifact, or the trauma to the wall of the bowel may have been severe. I raise this point because I wonder about the possibility that such a disease was present before the shunt and was related to the subsequent course.

The major problem in this case seems to be the events during the last few months before the seventh admission. When did the tendency to constipation begin — immediately after the shunt operation or a few months before the last admission?

Dr. Edgar B. Taft: All that was noted is that the patient had a tendency to be constipated and took mineral oil to have a daily bowel movement. He had constipation before he had the splenorenal shunt.

Dr. Culver: It is helpful to know the duration of the constipation because I have to decide whether the lesion that seemed to be partially obstructing the large bowel and the lesion that bled were related to the shunt operation and the previous condition or whether it was a new lesion. The fact that a large dose of Epsom salts caused pain that seemed to be fairly persistent makes me wonder if there was a partial obstruction. There were fairly severe cramps from the stimulating effects of the Epsom salts. The sudden appearance of bright-red blood in the stools and the increased number of bowel movements suggest that the obstructing lesion had

*Assistant physician, Massachusetts General Hospital.

†Ratnoff, O. D., and Patek, A. J., Jr. Natural history of Laennec's cirrhosis of liver: analysis of 386 cases. *Medicine* 21:207-268, 1942.

become ulcerated and started to bleed. This is confirmed by the fact that blood clots were seen coming from above during sigmoidoscopic study. If the findings at the second sigmoidoscopic examination are described in their entirety, and there was no granularity and no friability, the first sigmoidoscopic investigation, which raised the question of ulcerative colitis, is probably of slight importance. Not much ulcerative colitis seems to have been present, unless there was a localized lesion, perhaps in the upper loop of the sigmoid or in the descending colon, that was partially obstructing. Dr. Gibbons, can you shed any light on the nature of this lesion from the x-ray films?

Dr. Daniel S. Ellis: What made you raise the question of obstruction?

Dr. Culver: The patient had constipation, and there were cramps in the right side and across the lower abdomen; in the x-ray films, this area is narrowed.

Dr. John F. Gibbons: The original films twelve or more years before the last admission demonstrate the esophageal varices (Fig. 1*A*). The film of the abdomen, taken several years before the final admission, shows a large spleen. In this film, taken after the shunt operation, the varices have improved considerably. A spot film, taken on the last admission, gives very little evidence of residual varices (Fig. 1*B*).

Dr. Culver: In what percentage of cases have you seen varices improve and disappear like that?

Dr. Gibbons: I think this is a very unusual and dramatic response. Most of the time we see or think we see slight improvement after a shunt procedure. In the films of the last examination of the colon, a long segment of sigmoid is fixed to the area above it and to the right of the midline; this portion did not move before or after evacuation. Within the segment there is irregular, ragged mucosa that extends for about 15 cm. That is reproduced on all the films of the examination. The marked change in caliber of the colon starts above the rectosigmoid and involves the distal portion of the sigmoid up to the first loop (Fig. 2). Above this area the mucosa again assumes a normal appearance. The remainder of the colon proximal to this narrowing seems normal. This long segment of sigmoid is involved in a process that is most probably inflammatory; within the segment there are no intraluminal densities. Above the level of this sigmoid loop there are no abnormalities in the large bowel.

Dr. Ellis: Might that area of narrowing be due to spasm — a functional rather than an anatomic narrowing?

Dr. Gibbons: I am sure there must be some element of spasm, but it is so persistent and so equal in caliber over a period of three days that I think the narrowing is due primarily to thickening of the wall of the colon — that is, to organic narrowing and not to spasm.

Dr. Culver: Do you think that the ragged, saw-toothed edge of this narrowed area might represent ulceration?

Dr. Gibbons: Yes; I think this segment of bowel is ulcerated.

Dr. Culver: This leaves me with the problem of trying to decide whether the organic narrowing of the area of sigmoid was related to the cirrhosis, the shunt operation or a separate lesion. How could it have been related to the cirrhosis? Once in a while cirrhosis has been associated with ulcerative colitis, but then the ulcerative colitis is severe and appears before the cirrhosis. It seems unlikely that this patient had ulcerative colitis for as long a time as he had cirrhosis, because there was no evidence of a severe colitis.

Could there have been a mechanical disturbance of that area of bowel subsequent to the splenorenal shunt? Many adhesions were noted at the time of the operation, but they were higher in the abdomen. I cannot conceive that adhesions produced an inflammatory type of lesion in this area of the bowel.

That leaves me with what, to my mind, are the most logical possibilities: an inflammatory lesion or a neoplasm in this area that bled readily and apparently caused a great deal of blood loss. One has to postulate either a localized ulcerative colitis, perhaps of specific etiology, or else a carcinoma. In a man in this age group, although this is not the typical picture of carcinoma, it seems to me that without further evidence of ulcerative colitis I should have to put as my first choice carcinoma of the sigmoid and as my second a localized area of ulcerative colitis caused by a specific etiologic agent that I cannot name.

Dr. Edward B. Benedict: I cannot understand why Dr. Culver suddenly chose carcinoma.

Dr. Culver: With a ragged lesion in the sigmoid that is bleeding and causing obstructive symptoms, one always has to think of carcinoma.

Dr. Ellis: Would it not be unusual for a carcinoma to extend for so long a distance?

Dr. Culver: It might be, but I cannot conceive of anything else except ulcerative colitis that would give that sort of picture.

Dr. Ellis: Do you think a localized ulcerative colitis would cause that extensive hemorrhage?

Dr. Culver: It would be most unusual; that is why I put carcinoma first.

Dr. Ellis: You did not say anything about bleeding from the upper gastrointestinal tract except that it could happen.

Dr. Culver: I do not think that happened here.

Clinical Diagnosis

? Ulcerative colitis.
Cirrhosis of liver.

Dr. Perry Culver's Diagnoses

Carcinoma of sigmoid.
Cirrhosis of liver.

Anatomical Diagnoses

Varices of sigmoidal veins.
Postnecrotic cirrhosis.

Pathological Discussion

Dr. William V. McDermott: I did not see the operation, but I saw the patient postoperatively. At operation Dr. E. Stanley Crawford found that the entire sigmoid was extremely boggy and edematous, with huge, tortuous, dilated veins in the mesentery and around the bowel. The nature of this disease was not apparent even at operation, but it was obvious that the entire sigmoid loop was the source of the bleeding; therefore, a sigmoid resection from the descending colon down to the rectosigmoid was done. The extent of the resection made Dr. Crawford believe that it would be safer to do an end colostomy and to leave the distal bowel at the level of the pelvic floor turned down and nonfunctional. After the bowel had been resected the nature of the disease was still not apparent to anyone in the operating room.

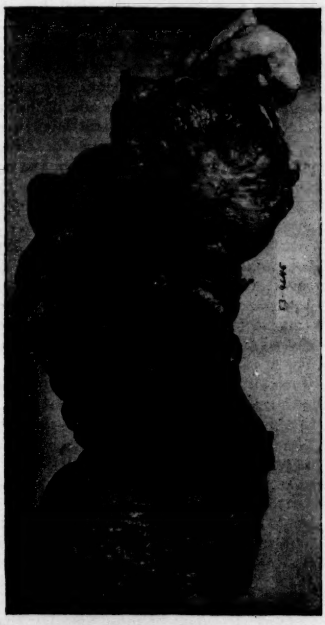

Figure 3.

Dr. Ellis: Did not Dr. Crawford believe it was ulcerative colitis before the bowel was opened?

Dr. McDermott: Yes; because of the edematous, boggy character of the entire sigmoid; the remainder of the bowel — the transverse and descending colon — that could be visualized was fairly normal. The postoperative course was interesting in that the patient went into deep coma after about twenty-four hours, with marked elevation of the ammonia level; in the next forty-eight hours he received sodium glutamate intravenously, the ammonia level returned to normal, and he awoke. Since then he has been discharged without further difficulty.

Dr. Taft: In the wedge of liver that we received there was a large area of scarring, with numerous finer strands of scar tissue. There were irregularly shaped lobules of liver, some of which had quite normal anatomy and some of which showed localized proliferation, all of which are consistent with postnecrotic cirrhosis. In the specimen of rectosigmoid (Fig. 3) the mucosal changes were largely confined to an area 6 or 7 cm. in length, which showed peculiar raised submucosal nodules. The remainder of the bowel was not particularly abnormal in appearance. About the nodule the mucosa was quite granular, and the character of the mucosal folds are consistent with that seen in chronic idiopathic ulcerative colitis. Microscopically, the mucosa as far as we could see was intact; it was, however, quite atrophic. There were some dilated glands in areas and a very minor chronic inflammation. The startling finding, which was also seen grossly on dissection, was the extreme dilatation of the veins beneath the mucosa of the bowel. These varices had the appearance of hemorrhoids and were localized to this portion of the sigmoid. One of the nodules noted grossly (identified by safety pin in Fig. 3) was a thrombosed varix.

It is difficult to explain such varices from the standpoint of the anatomy of the region. Dr. Robert R. Linton said that he had never heard of varices in this part of the bowel. I do not recall ever seeing one. It is possible that there was a minor anomaly of venous circulation of the large bowel. Ordinarily, the superior hemorrhoidal vein and the sigmoidal vein join together to form the superior mesenteric vein, which drains into the portal vein. It is possible that the inferior part of the sigmoidal vein became involved with varicosities in the patient as the hemorrhoidal veins do in patients with increased pressure in the portal vein although we have never seen that particular complication before.

Dr. Culver: You would not know this because this was not a post-mortem examination, but I wonder if there was thrombophlebitis in the portal bed.

Dr. Taft: I do not know. There were thrombi in some of the dilated veins that might suggest that, but most of the veins were only dilated and congested, without thrombosis. Although the mucosa was apparently intact, the bleeding was almost certainly from a ruptured varix that collapsed and could not be identified after surgical removal. This is not too surprising when one considers how seldom the bleeding points in bleeding esophageal varices can be identified post mortem.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

MODIFIED AFFILIATION PROGRAM

IN its issue of January, 1953, the *Harvard Medical Alumni Bulletin* discussed in some detail the steps then being taken to reactivate "on paper" the Fifth General Hospital, affiliated with the parent medical school as the latter's contribution to the Army of the United States in the event of another world war or major national emergency.

A recent communication from the Office of The Surgeon General, dated January 19, 1954, indicates that the new or "modified" affiliation plan of the Department of the Army has been accepted by more than 50 medical colleges and large civilian hospitals. The modified plan, as the term implies, differs in important details from the one heretofore prescribed, although in each case a 1000-bed general-hospital unit will ultimately result. The differences lie in the methods of commissioning officer personnel and of initial activation or calling to duty of the unit. These differences, it is believed, will make more civilian physicians and dentists willing to be considered for staff positions in such a unit and will make more potential sponsoring institutions accept the task implied in their sponsorship.

The modified plan requires the sponsor to supply only 6 officers at the time the Army calls the affiliated unit to active duty. These officers comprise 1 chief nurse and 1 other nurse of the Army Nurse Corps; 2 captains of the Medical Corps; 1 captain of the Dental Corps; and 1 dietitian first lieutenant of the Women's Medical Specialist Corps. This group will join the remainder of the headquarters and administrative complement at the post or station of activation for preliminary organizational work and training in military procedure.

Whereas the Army will furnish the rest of the headquarters and administrative complement, the sponsor will be charged with furnishing at least the "key specialists" for the professional complement, the latter not to be called to duty until "several months" ("D-Day plus one year," according to the understanding of the *Alumni Bulletin* cited above) after the unit is initially activated. It is not entirely clear what is meant by key specialists: from the military point of view key personnel would indicate responsible chiefs of services and sections of the professional division of a general hospital, but from the medical point of view the key personnel referred to may be considered as strictly medical or dental specialists.

At all events, during the several months to a year after activation of the initial echelon of the unit the sponsor will select the members of the staff required to fulfill its obligation. Time will be available, it is implied, for these members to prepare and submit their applications for commissions in grades appropriate to the positions they are to fill. When commissions are granted they will be in the Army of the United States only, and not in the Reserve — a point of importance in assuring the temporary officer of a clean break with his military past when the emergency is at an end.

It therefore seems that the modified plan grants to the sponsor and to the members of the sponsored

unit a flexibility not available in the older plan; that there will be a considerable lapse before high-ranking staff members of the civilian hospitals and medical schools are called to duty after the initial emergency has been declared; and that the professional complement as a whole will not be placed in uniform until there is need for its professional services in an active Army general hospital.

This is certainly a change from the pre-existing policies. It should ameliorate to a considerable degree the unhappiness hitherto engendered by long periods of purely military training in advance of utilization of the unit for its primary function. It will allow for commissioning civilian specialists in grades commensurate with the duties to be assumed by them in the military service. The only persons concerning whom there may be advance misgivings along these lines seem to be the two captains of the Medical Corps and the captain of the Dental Corps, who must be the only "minute men" of the organization.

After the unit takes the field it will be quite as much a part of the Army of the United States as any tactical or service unit of the Regular Army. Its officers will be quite as much under military law as any graduate of West Point. No matter how much the doctor in uniform yearns to limit his activities to the practice of his profession in general or his specialty in particular he cannot divorce himself from a greater or smaller amount of purely administrative work, and, of course, he cannot be protected from being charged with one or more disparate functions "in addition to his regular duties." In the matter of promotion he will find himself frustrated at times by the old stumbling blocks of age-in-grade requirements and lack of vacancies in the table of organization under which he is serving. Finally, the uncertainties inherent in field service will not allow him a complete guarantee of finishing the war with the unit in which he starts.

Whether the modified affiliation plan will serve its purpose effectively under the blitzkrieg conditions almost certain to be inherent in the outbreak of the "next war" remains to be seen. But then it will become an infinitesimal factor in the whole overwhelming and ominous picture that is veiled in the future.

TREATMENT AND PREVENTION OF BACTERIAL ENDOCARDITIS

THE greatest triumph in therapeutics in this century has been in the cure of many infectious diseases by antimicrobial agents. The life-saving achievements of these antibiotic and chemotherapeutic agents are most conclusively demonstrated in diseases that, before their advent, were nearly always fatal, notably in meningitis and in bacterial endocarditis. To be sure, these patients represent only a minute fraction of those receiving antimicrobial therapy, but they constitute a group in which the most intensive efforts, properly directed, are the most rewarding. This is well illustrated in the treatment of bacterial endocarditis.

The current status of many aspects of the diagnosis, treatment and prevention of bacterial endocarditis is reviewed in considerable detail in the present and the preceding issue of the *Journal*. Much confusion has resulted from the availability of many dosage forms of penicillin, the many antibiotic regimens recommended for this agent, the increasing number of additional antibiotics that have become available and have been employed singly and in various combinations, the importance and difficulties of treatment of patients with negative blood cultures and the problems involved in prevention. The literature bearing on these and other aspects has been critically analyzed, and although final answers are not given to all the questions raised, an attempt is made to put the available data in their proper perspective, to present deductions concerning the optimum methods of using the available agents and to point out the areas in which further data are sorely needed.

Two practical points are particularly worthy of comment. The first is the paramount importance of etiologic — that is, bacteriologic — diagnosis for the proper management of all cases of bacterial endocarditis. For the physician who is not practicing within the confines of a well equipped hospital or not having easy access to a good bacteriologic laboratory, this aspect seems almost forbidding, and some consider it impractical and useless. And yet there is hardly any condition in which maximum effort in this direction is more warranted and more rewarding but in which failure to make such an effort is more likely to result in tedious and expensive

floundering in search for the proper therapy to achieve a successful outcome.

The clinical diagnosis can readily be suspected in a large majority of cases, but, since the treatment must be long, intensive and costly even when properly directed on the basis of accurate bacteriologic diagnosis, it seems only reasonable to expect the physician to avoid, as far as possible, embarking on such a therapeutic program blindly. Improper and inadequate treatment accounts for the majority of failures in bacterial endocarditis, and optimum therapy is hardly possible without knowledge of the offending organism and its susceptibility to the available antibiotics.

The second aspect worthy of comment concerns the prophylaxis of bacterial endocarditis in patients with heart disease. The points at issue are boldly presented in this review, but they have been more colorfully discussed in the correspondence columns of the *British Medical Journal*, where some readers are permitted to "blow off steam" but where others have been known to "cast off pearls" in the course of their comments on opinions expressed by various authors. In a paper published in that journal, Christie[1] recommended that patients with rheumatic fever or congenital heart disease be given 500,000 units of penicillin daily for three days, beginning one or two hours before tooth extractions or other focal operations. The dose, as noted by Christie, was based not on clinical trial but on an intelligent guess made when penicillin was in short supply.

In commenting on this recommendation, Coffin[2] stated that he could not understand why, fully aware of the disastrous nature of bacterial endocarditis and of the harrowing nature of its treatment, Christie did not insist on heavy doses for several days before the operation in an attempt to reduce the number of bacteria in the foci before they were stirred up and disseminated by the operation. He agreed that treatment should continue after the operation as well, but he described Christie's method as "very much like locking the stable door after the horse (or the bacteria) has bolted."

In reply to this comment Garrod[3] cited the case reported by Christie, Cates and himself, in which subacute bacterial endocarditis due to a relatively penicillin-resistant streptococcus followed the use of heavy doses of penicillin prophylactically before and after a tooth extraction. He pointed out that large doses, with excretion of high concentrations into the saliva before the operation, cause replacement of the oral flora by resistant organisms, which may then give rise to bacterial endocarditis that is difficult to cure. He therefore recommended a dose of procaine penicillin two hours before the operation and of sodium penicillin five minutes after as a preferable method of prophylaxis, noting that "So far from this being an example of locking the stable door after the horse has bolted, what Mr. Coffin would have us do may be likened to opening the lion's cage instead of the jackal's."

To be sure, the case cited by Garrod, which has been made into a *cause célèbre*, may be unique. However, the entire controversy, as also brought out in Finland's review, serves clearly to point up the need for carefully controlled and authenticated data on the value of various types of antibiotic prophylaxis of bacterial endocarditis and, indeed, of any other infections.

Of interest in this connection is the recent report of a case of subacute bacterial endocarditis that followed extraction of a tooth during continuous prophylaxis with intramuscular injection of benzathine penicillin G (Bicillin).[4]

References

1. Christie, R. V. Subacute bacterial endocarditis. *Brit. M. J.* 2:438, 1953.
2. Coffin, F. R. Subacute bacterial endocarditis. *Brit. M. J.* 2:571, 1953.
3. Garrod, L. P. Endocarditis and dental extraction. *Brit. M. J.* 2: 727, 1953.
4. Stollerman, G. H., Rusoff, J. H., and Hirschfeld, I. Prophylaxis against group A streptococci in rheumatic fever patients by use of single, monthly injections of N,N′ dibenzylethylenediamine dipenicillin G (Bicillin). In *Antibiotics Annual, 1953-1954*. Edited by H. Welch and F. Marti-Ibanez. 632 pp. New York: Medical Encyclopedia, Incorporated, 1953. Pp. 114-118.

NATIONAL FUND FOR MEDICAL EDUCATION

Some degree of confusion being a natural tenant of the human mind, many persons, not excluding physicians, still find some difficulty in differentiating the National Fund for Medical Education from the American Medical Education Foundation. Working toward an identical goal, the former has the broad and practical philanthropic purpose of obtaining grants for the country's medical schools from whatever generally nonmedical source that can be made to see where its own interest lies in this vital matter, whereas the latter, established by the American Medical Association and working closely with the Fund, has for its object the solicitation of funds from the medical profession itself.

One of the ways in which the Medical Advisory Committee of the National Fund is seeking to

spread its gospel is through local conferences "to bring together a number of medical school deans and a group of physicians in industry to explore ways to strengthen the link between academic and environmental medicine so that medicine may better serve industry and the public." Three such regional meetings have so far been held — in New York City, in Pittsburgh and most recently in Boston.

These meetings are intended to serve two general purposes of medicine. The first is to promote discussion of curricular problems of teaching, especially as they apply to "environmental medicine," which is the new term for medicine in industry. The second is to find ways in which the leaders of industry can themselves be made aware of the ways whereby medicine serves them, and the necessity of supporting the training of physicians. The essentially self-interested character of business makes it obligatory to demonstrate to it that the care of the worker is a paying proposition and that such care can become a perpetually effective process only so long as a perpetual stream of physicians comes off their own assembly line.

Any failure so far to impress industrial management with the logic of this argument is the failure that medicine has too often encountered in its attempt to establish good public rapport in general. It is based on medicine's inability to overcome the reticence imposed by its ancient taboo against speaking out in public, of proclaiming its purposes and of publicizing its services. It has been that failure of communication that has made it almost universally misunderstood by its public.

Now it must speak out if an essential service is not to languish. Consistent failure in the support of medical education will result not so much in its grinding to a halt as in its slow attenuation. Most schools will at first simply curtail the quality of their instruction; others will fade from the picture rather than allow their quality to suffer too greatly. It is a problem that can hardly be solved by the establishment of new schools that must in turn be supported from the nation's economy.

BRAIN WATCHER'S MANUAL

With the recent chastening denouement regarding the Piltdown man at least partly in mind, it is interesting to note in a December, 1953, release from the University of Wisconsin News Service that "there are monkeys on the University of Wisconsin campus who don't know it, but their brains are showing."

An impulsive reaction, of which a variety are available, is to be avoided. The observation that such a statement need not be limited to the University of Wisconsin is not only superfluous but impertinent. To say that hats had better be worn on college campuses as well as in the Harvard Yard would be flippant, and a remark such as "What brains?" would be unkind and unwarranted.

The fact, of importance to science, is that University of Wisconsin investigators have developed a successful technic of trephining animals' skulls and sealing into the opening a plastic window through which the brain can be observed, in all its subtle activities. Through this judas window the reactions of at least the cortex to various stimuli can be surveyed, even if the thoughts beneath the surface cannot yet be revealed.

The opportunities for future development seem unlimited. When the cortical barrier is finally passed and a mechanism developed for opening and closing the window at will, then perhaps ideas themselves may be inspected at their point of origin or new and better ones introduced. It may even be that the western world's insistent neighbors, the Soviets, having anticipated western progress in the invention and production of such modern devices as the telephone, the automobile and the airplane, are already employing the ingenious technic described above in the operation of their well known cerebro-laundromats. From brain watching to brain washing may be but a single step.

Transactions of the American Medical Association. — *Volume VI. of this publication, to which we have before alluded, is of rare value to the American medical brotherhood.* ******* *In order to keep up with the history of medicine in our own country, this is the book to have in a library.*

Boston M. & S. J., *March 15, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

ROBEY — William H. Robey, M.D., of Boston, died on February 23. He was in his eighty-fourth year.

Dr. Robey received his degree from Harvard Medical School in 1895. He was clinical professor of medicine, emeritus, Harvard Medical School, consulting physician, Boston City Hospital, and a member of the staffs of the Milton, Marlboro and Norwood hospitals. He was formerly president of the Massachusetts Medical Society, the American Heart Association and the New England Heart Association and was a member of the American Clinical and Climatological Association and a fellow of the American College of Physicians and the American Medical Association.

He is survived by his widow, a son, four grandchildren and six great-grandchildren.

BOSTON MEDICAL LIBRARY

USE OF FACILITIES

Any responsible person may become a member of the Boston Medical Library; its facilities are available to the general public.

Fellows and members of the Library, including all the fellows of the Massachusetts Medical Society, professional members, student members and postgraduate members, and all libraries throughout New England are eligible to borrow books.

Fellows and members may obtain books most easily by writing to the Library, 8 Fenway, Boston 15, giving the title and author of the book or pamphlet desired. Wrappers in which books are shipped will have the return address on the reverse side and should be preserved.

NONCLINICAL NOTES

WEST ROXBURY VETERANS ADMINISTRATION HOSPITAL

The West Roxbury Veterans Administration Hospital has been reopened to accommodate 150 general medical and surgical patients and 150 paraplegic patients. Dr. Richard Warren is chief, Surgical Service; Dr. Thomas A. Warthin, chief, Medical Service; and Dr. Herbert S. Talbot, chief, Paraplegia Service and Urological Section.

The teaching staff is under the supervision of the Boston Deans' Committee and will be associated with Harvard Medical School. (The Veterans Administration Hospital on South Huntington Avenue has a similar connection with the medical schools of Boston University and Tufts College.)

NOTICES

ANNOUNCEMENT

Dr. Edward Budnitz announces the removal of his office from 44 Cedar Street, Worcester, to 37 Fruit Street, Worcester, as of April 1.

TUFTS MEDICAL ALUMNI DINNER MEETING

The annual dinner meeting of the Tufts Medical Alumni Association will be held at the Hotel Somerset, Boston, on March 31, at 6:30 p.m. The guest speaker will be Dr. Arthur S. Flemming, director of the Office of Defense Mobilization. Other speakers will include Dr. Nils Y. Wessell, president of the college and Joseph M. Hayman, Jr., M.D., dean of the medical school.

There will be open house at the medical school from 10:30 a.m. to 4:00 p.m.

BOSTON CITY HOSPITAL SEMINAR ON PERIPHERAL VASCULAR DISEASE

A seminar on peripheral vascular disease will be presented in the Cheever Amphitheater, Boston City Hospital, by the Third Surgical Service (Boston University) of the Boston City Hospital on March 31. Dr. Eugene E. O'Neil is chairman. All physicians are cordially invited.

PROGRAM

9:30 a.m. Treatment of the Post-Phlebitic Syndrome. Dr. John J. Byrne, Boston University School of Medicine.

10:00 a.m. Buerger's Disease. Dr. Edward A. Edwards, Peter Bent Brigham Hospital.

10:30 a.m. Treatment of Arterial Emboli. Dr. George F. Miller, Boston University School of Medicine.

11:00 a.m. Raynaud's Disease. Dr. Charles W. Robertson, Boston University School of Medicine.

11:30 a.m. Treatment of Acute Vascular Injuries. Major Edward J. Jahnke, Walter Reed Army Hospital.

2:00 p.m. Lumbar Sympathectomy in Obliterative Arterial Disease. Dr. Reginald H. Smithwick, Boston University School of Medicine.

2:30 p.m. Intimectomy and Autogenous Vein Grafts for Segmental Arterial Occlusions. Dr. Gerald H. Pratt, New York University–Bellevue Medical Center.

3:00 p.m. Arterial Grafting in Peripheral Arterial Disease. Dr. Charles A. Hufnagel, Georgetown University Medical School.

3:30 p.m. Blood-Vessel Grafts in the Surgical Treatment of Diseases of the Major Arteries. Dr. Robert R. Linton, Harvard Medical School.

4:00 p.m. Use of Fresh and Preserved Grafts for Aneurysms or Obstructive Arterial Lesions. Dr. Ralph A. Deterling, Jr., Columbia University College of Physicians and Surgeons.

BOSTON COMMITTEE ON ALCOHOLISM

A special meeting of the Boston Committee on Alcoholism will be held for physicians and industrial managers at the Harvard Club on March 24 at 6:30 p.m. Dr. R. Gordon Bell will speak on the topic "Clinical Orientation to Problem Drinking." The discussers will be Dr. Frank W. Barden, president, New England Industrial Medicine Society, and William R. Hayes, American Society of Personnel Administrators. Dinner reservations should be made in advance (charge, $3.50).

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

The spring clinical assembly of the Massachusetts Academy of General Practice will be held at St. Luke's Hospital (morning session) and the New Bedford Hotel (afternoon and evening session) in New Bedford, on April 7. The program is as follows:

8:30 a.m. Medical films.

10:00 a.m. Malignant Tumors of the Rectum and Colon. Dr. Milton T. MacDonald, St. Luke's Hospital.

10:40 a.m. Diseases of the External Genitalia. Dr. Howard Hoffman, St. Luke's Hospital.

11:00 a.m. X-Ray Treatment of Acute Bursitis. Dr. Emory Lewis, St. Luke's Hospital.

11:20 a.m. What About Quinidine? Dr. Harold Cantor, St. Luke's Hospital.

11:40 a.m. Pheochromocytoma: Personal case history. Dr. Walter Mindus, St. Luke's Hospital.

2:30 p.m. Panel on cortisone and ACTH. Drs. Robert P. McCombs (chairman), James F. Patterson and Henry A. Mosher, Pratt Diagnostic Hospital.

3:45 p.m. What Can Bronchoscopy Do for the General Practitioner? Dr. Chevalier L. Jackson, Temple University.

8:00 p.m. The Place of the General Practitioner in Future Medicine. Dr. Donald M. Clark, member of the Magnuson Commission.

During the morning and afternoon sessions there will be a special program for wives of physicians.

EXAMINATION FOR PUBLIC HEALTH SERVICE MEDICAL OFFICERS

A competitive examination for appointment of medical officers to the Regular Corps of the United States Public Health Service will be held on June 1, 2 and 3. Examinations will be held at a number of points throughout the United States, located as centrally as possible in relation to the homes of candidates. Applications must be received before April 30.

Application forms and additional information may be obtained from the Chief, Division of Personnel, Public Health Service, Department of Health, Education, and Welfare, Washington 25, D. C.

SCHERING AWARD COMPETITION

Students in the United States and Canada are invited to submit papers for the Schering Award for 1954 on one of three topics: use of androgen therapy in the female; prophylactic and therapeutic uses of parenteral antihistamines; and modern treatment of infectious and allergic disorders of the eye. Students may compete individually or in teams. Entry forms specifying the chosen subject must be submitted before July 1, and manuscripts before October 1. The first prize is $500, and the second $250. Information and instructions may be obtained from the Schering Corporation, 2 Broad Street, Bloomfield, New Jersey.

AMERICAN SOCIETY OF MEDICAL TECHNOLOGISTS

The twenty-second annual national convention of the American Society of Medical Technologists will be held at the hotels Delano and DiLido, Miami Beach, June 13 through 17.

SOCIETY MEETINGS AND CONFERENCES

March 15–26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

March 15, April 5 and 19. Hartford Medical Society. Page 1130, issue of December 31.

March 16. South End Medical Club. Page 399, issue of March 4.

March 16–31. Consultation Clinics for Crippled Children. Page 305 issue of February 18.

March 16, April 8 and 20. Boston City Hospital House Officers' Association. Page 265, issue of February 11.

March 17. New England Society of Physical Medicine. Day Room, Robert Breck Brigham Hospital, 125 Parker Hill Avenue, Boston. 8:00 p.m.

March 20, April 17 and May 15. Massachusetts Hospital School. Orthopedic Rounds. Page 265, issue of February 11.

March 22. Phi Delta Epsilon Fraternity Graduate Club of Boston. Page 399, issue of March 4.

March 22–25. American Academy of General Practice. Page 129, issue of January 21.

March 24. Middlesex East District Medical Society.

March 24. Boston Committee on Alcoholism. Page 443.

March 26–May 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

March 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

March 28. National Gastroenterological Association. Page 265, issue of February 11.

March 31. Boston City Hospital Seminar on Peripheral Disease. Page 443.

March 31. Tufts Medical Alumni Dinner Meeting. Page 443.

March 31–April 2. American College of Surgeons. Sectional Meeting. Page 266, issue of February 11.

April 7. Massachusetts Academy of General Practice. Page 443.

April 8–11. International Academy of Proctology. Page 130, issue of January 21.

April 9. New England Society of Anesthesiologists. Page 399, issue of March 4.

April 10. American Congress of Physical Medicine. Page 266, issue of February 11.

April 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

April 21–24. Seminar and Conference on Cancer Cytology. Page 346, issue of February 25.

April 29, 30 and May 1. American Goiter Association. Somerset Hotel, Boston.

May 1. State University College of Medicine at New York City. Alumni Association. Page 400, issue of March 4.

May 11. Middlesex East District Medical Society. Annual Meeting. (Harlow Dinner.)

May 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.

May 12. New England Obstetrical and Gynecological Society. Spring Meeting. Longmeadow Country Club, Springfield.

May 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

May 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

May 31–June 3. American Urological Association. Page xvii, issue of July 23.

June 5 and 6. International Association for the Study of the Bronchi. Page 400, issue of March 4.

June 13–17. American Society of Medical Technologists. Notice above.

June 17–19. American Geriatrics Society. Page 266, issue of February 11.

July 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

July 23–29. International Cancer Congress. Page 914, issue of November 26.

July 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.

September 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

September 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MARCH 18

THURSDAY, MARCH 18

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m. Thoracic Conference. Evaluation of the Functions of the Lung. Dr. T. Richard Watson, Jr. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.–2:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Reflections on Surgery of the Mitral Valve. Dr. Samuel A. Levine. Stearns Auditorium, New England Center Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, MARCH 19

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Drs. Proger, Hayman, McCombs, Astwood and other members of the Medical Staff. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

(Notices concluded on page xxxix)